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**IMPLEMENTATION OF
COMPULSORY LICENSING OF
PHARMACEUTICALS IN THAILAND**

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DECLARATION

I, Adun Mohara, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: 

Date: 21 November 2017

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ABSTRACT

Intellectual property rights (IPRs) play an important role in creating incentives for innovations. To strengthen and harmonise global standards of IPRs, the WTO members established the international agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) and provided flexibilities for governments to safeguard social benefits of their countries. Compulsory licensing (CL) is one of the flexibilities under TRIPS that enables a government authority to use the licenses of patented medicines without patent-holders' permission. However, policy makers in many countries are reluctant to use CL to promote access to essential medicines. One explanation is that most countries are worried about the potential implications of using the policy, and they are uncertain about which implementation strategies might help avoid negative consequences.

The aim of this PhD thesis is to propose a framework to aid decision-making and implementation of drug policy, focusing on CL under the condition of public non-commercial use and government use of license. This framework is designed to be used as a tool for policy makers in the Thai Ministry of Public Health, suggesting a list of policy elements to help them consider related elements for policy action in making a decision and implementing CL policy in order to minimise negative consequences of the CL. Mixed methods were employed to develop the framework. This study began by developing a preliminary framework based on generic elements of CL policy suggested by inter-governmental organisations. The preliminary framework was strengthened by incorporating lessons learnt from experiences of the former government of Thailand. The implications of CL policy decisions on certain drugs were evaluated in terms of lifetime cost savings compared across different drug types. This allowed the identification of key factors to be included in criteria for drug selection. In addition, the performance of the Thai government in policy implementation was evaluated in order to prioritise areas for improvement. Finally, the contents of the preliminary framework were assessed in terms of applicability to the Thai context. Any additional elements derived from experiences of the former government were used to strengthen the framework.

The findings of this study suggest key elements, which should be included in the framework to aid decision-making and implementation of drug policy, focusing on CL policy. 32 elements were identified to be included in the framework. This study also suggests strategies for the decision-making process. Three additional factors are suggested to be incorporated in the drug selection criteria, in order to help policy makers to select the drugs that potentially create the greatest benefits from CL implementation. In addition, this study suggests strategies for the implementation process. The findings help prioritise four implementation areas, which should receive more attention within current CL implementation. This study closes with policy recommendations for the Thai government about the current and future use of CL policy to improve its performance, and also for other countries having the similar context to learn from the Thai experiences.

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ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ARVs	Antiretroviral drugs
CL	Compulsory licensing
CML	Chronic myeloid leukaemia
CPG	Clinical Practice Guidelines
CPI	Consumer price indexes
CSMBS	Civil Servants Medical Benefits Scheme
DDC	Department of Disease Control
DIP	Department of Intellectual Property
DMSIC	Drug and Medical Supply Information Centre
FDA	Food and Drug Administration
FDI	Foreign Direct investment
GDP	Gross Domestic Product
GIPAP	Glivec International Patient Assistance Program
GIST	Gastro-intestinal Stromal Tumours
GMP	Good Manufacturing Practice
GPO	Government Pharmaceutical Organization
GSP	Generalized System of Preferences
HICs	High Income Countries
HISRO	Health Insurance Systems Research Office
HITAP	Health Intervention and Technology Assessment Program
HIV	Human immunodeficiency virus
IDV/r	Indinavir & ritonavir combination
IHPP	International Health Policy Program
IPRs	Intellectual Property Rights

LPV/r	Lopinavir & ritonavir combination
LMICs	Low and Middle Income Countries
MFA	Ministry of Foreign Affairs
MOC	Ministry of Commerce
MOPH	Ministry of Public Health
NGO	Non Government Organization
NHSO	National Health Security Office
NLEM	National List of Essential Medicines
NSCLC	Non-Small Cell Lung Cancer
PhRMA	Pharmaceutical Research and Manufacturers Association of American
PI	Parallel Import
PWL	Priority Watch List
QALY	Quality Adjusted Life Years
R&D	Research and Development
RDU	Rational Drug Use
SSS	Social Security Scheme
TRIPS	Trade Related Aspects of Intellectual Property Rights
UC	Universal Coverage
UNDP	United Nations Development Programme
USA	United State of America
USTR	United States Trade Representative
VMI	Vendor Managed Inventory
VL	Voluntary Licensing
WHO	World Health Organisation
WIPO	World Intellectual Property Organization
WTO	World Trade Organisation

Chapter 1: Introduction

Intellectual property rights (IPRs) are a legal agreement, which acknowledges exclusive rights to creations of the mind. According to intellectual property law, innovators are granted exclusive rights to protect their intangible assets. The aim is to create incentives for innovations in research and development (R&D) [1]. Patents are a form of IPR approved by a sovereign state. They give exclusive rights to an innovator for a limited time period, in exchange for the public disclosure of the innovation. The exclusive right is granted to a patent owner to prevent others from exploiting, producing, selling, or distributing the patented invention without permission from the patent owner. The degree of exclusive rights and the practice for granting patents differ between countries according to domestic laws and international agreements [2].

The international agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) was established by World Trade Organization (WTO) members in 1995 as the most comprehensive multilateral agreement on IPRs [3]. For a variety of industrial sectors, such as computer software, pharmaceutical and agricultural innovations, strengthened and harmonised global IPR standards are necessary to internationally warrant innovations. TRIPS obligatorily require member countries to recognise patent protection in almost all fields of technology, and the agreement states that patent protection must be offered to innovative inventions for at least 20 years and covered for both products and production processes [4].

IPRs and patent protection play an important role in the development of pioneering technology and the global economy. The benefits of patenting are recognised as an instrument to promote innovative knowledge and technological advancement, which are essential factors for economic growth [5]. Patenting is used to promote global economic growth by transferring know-how and expertise from developed countries to less developed ones through international trade and foreign direct investment (FDI). One study found that the strength of IPR protection in low and middle income countries (LMICs) seemed to have a considerable effect on the extent of direct investment, particularly in high-technology industries from

American, Japanese and German firms, although the size of the effects differed from industry to industry [6].

Patenting in pharmaceutical products is more complicated than other pioneer products. Being a high-technology industry, pharmaceutical manufacturing requires a substantial investment in the product development process. Evidence shows that annual expenditures for pharmaceutical R&D of new drug approvals during 1994 and 2000 ranged between US\$ 400 million and US\$ 1 billion [7, 8]. However, only 11% of investments were successful in developing a high quality, safe and efficacious product for treatment in people [9]. As a result, prices of pharmaceutical products seem to be relatively higher than other technologies. Patenting enables pharmaceutical firms to sell a patent drug at a monopoly price in order to compensate their R&D costs, thereby providing industrial incentives for pharmaceutical innovation [10].

However, the private interests of profit and cost-covering need to be assessed in the context of public health interests. As outlined above, offering IPRs and patents is an incentive for R&D, but can also result in monopoly prices that are sometimes beyond the ability to pay of patients and governments in poor countries. Evidence shows that in the late 1990s, despite the rising death and morbidity rates of HIV/AIDS, prices of patented antiretroviral drugs (ARVs) increased by 200-300% [11, 12]. Therefore, at that time, there was concern that private incentives needed to be balanced with ethical issues of patients' access to patented medicines [13].

The 1995 TRIPS agreement provided flexibilities that allowed governments to safeguard social benefits for their countries [14]. Compulsory licensing (CL) is one of the flexibilities under TRIPS that enables a government authority to use licenses of patented products, including medicines, without patent-holder permission [15]. A number of conditions were formulated for governments to make exceptions to patent owners' rights, including "national emergencies", "other circumstances of extreme urgency", "public non-commercial use" (or "government use"), or "anti-competition" [16]. In addition, countries are permitted to determine the grounds upon which licenses are granted, as well as what constitutes a national emergency and circumstances of extreme urgency [17].

It has been acknowledged that the costs of treatment with patented medicines are unaffordable to some governments, especially in LMICs. Sometimes the purchase of expensive, patented medicines could threaten the sustainability of government-provided health services. In order to address this problem, some countries have decided to apply the CL policy to manufacture or import cheaper generic medicines. However, policy makers in many countries are reluctant to use CL to promote access to essential medicines. Beall *et al.* found that only few LMICs made use of this CL policy between 1995 and 2010, and the trend of documented CL episodes declined during the fifteen-year period [18]. Possible explanations for the decline in use of CL is that most countries are worried about potential political and economic retaliations [19, 20]. Based on my best knowledge, there is no concrete framework, which suggests strategic approaches to optimise benefits and minimise cost when the policy is implemented.

In this PhD thesis, I will address this topic through focusing on the case of Thai CLs. The former Minister of Public Health, Dr. Mongkol Na Songkla, decided to implement CL policy in the condition of “public non-commercial use or government use of license” in order to promote access to essential drugs for Thai people. The former government aimed to issue CL policy for seven medicines, including two ARV drugs for treatment of HIV/AIDS (efavirenz and LPV/r), one drug for treatment of cardiovascular disease (clopidogrel), and four drugs for treatment of cancer (letrozole, docetaxel, erlotinib and imatinib). However, only five drugs (efavirenz, LPV/r, clopidogrel, letrozole, and docetaxel) have been implemented under CL policy in Thailand. During the CL implementation period, there were a number of unanticipated events in the Thai CL for the said drugs. Policy insights derived and lessons learnt from experiences of the former government could be of value for developing a framework. The framework suggests key elements to be considered for decision-making and implementation of drug policy, focusing on CL policy, in order to optimise the benefits and minimise negative consequences of the policy.

1.1 Thesis aims and objectives

The aim of this PhD thesis is to develop a framework for decision making and implementation of drug policy, focusing on CL policy under the condition of public non-

commercial use or government use of a license. The framework is designed to be used as a tool for policy makers in the Thai Ministry of Public Health by providing a list of policy elements that could help optimise benefits of the policy. It is a descriptive framework that seeks to be comprehensive in encompassing all elements of concern in CL policy. The framework does not provide an analytical explanation or rationale for decision making and implementation. The policy elements include:

- Activities and supportive instruments required to implement the policy,
- Actors required to participate in the policy process,
- Contextual factors required to support the policy implementation,
- And other implementation strategies to improve policy performance and implications.

In this study, I propose a framework to aid decision-making and implementation of drug policy, focusing on CL policy based on experiences of the former government of Thailand. This study began with the development of a preliminary framework based on generic recommendations from literature published by intergovernmental organisations. It was strengthened by an investigation of the experiences of the former government, in terms of implications of the decisions to issue CL on different drug types, and the implementation of the policy during 2007 to 2014. Finally, the applicability of the framework was assessed through qualitative approaches. The four study objectives are as follows:

Objective 1: To develop a preliminary framework to aid decision making and implementation of drug policy, focusing on CL policy.

Objective 2: To estimate life time treatment cost savings due to implementation of CL for five drugs against HIV/AIDS, stroke and cancer.

Objective 3: To analyse the performance of the Thai government in implementation of CL policy in terms of drug procurement, drug substitution at health care facilities, and drug access among patients.

Objective 4: To assess the applicability of the framework in Thailand.

1.2 Outline of the thesis

This thesis is organised into nine chapters. Chapter Two gives background to CL policy. A literature review was conducted to explore situations leading to the use of CL policy and implications of such CL use in LMICs. Chapter Three provides background information on Thailand in terms of the health care system and political issues surrounding CL policy. Chapter Four gives an overview of the research methodology for each objective.

In Chapter Five, a framework was initially developed by analysing policy elements that affect CL policy decision and implementation. The framework was classified into four stages, including agenda setting, policy formulation, policy implementation and policy monitoring. The first two steps belong to the decision-making process, while the others belong to the implementation process. I conducted a literature review to identify policy elements that should be included in each stage of the CL policy process. All identified elements were retrieved from generic recommendations of intergovernmental organisations such as the WTO and WHO. In the next chapters, the preliminary framework was strengthened through investigation of the experiences of the former Thai government when implementing the policy.

In chapter six, the implications of CL policy implementation for the five drugs were estimated in monetary terms. The implications were analysed in terms of benefits from a reduction in lifetime treatment costs among patients receiving the five drugs under CL policy. The comparative benefits across different drug types were used to identify key elements, which should be incorporated in the drug selection criteria in order to gain the highest benefits from CL implementation. The findings could be used to help develop drug selection criteria to be included in the framework of CL policy.

In chapter seven, the performance of CL policy implementation was evaluated to identify key elements, which should be considered by policymakers and authorised agencies for improving the policy performance. In this study, the CL policy performance is classified into three sections: drug procurement, generic drug substitution for its patented versions, and drug access improvements. Achievements of policy implementation in each section were analysed. If there was any failure to such achievement, the costs from defective performance or unanticipated results

were analysed in monetary terms. The findings could be used to help prioritise areas, which should receive more attention within current CL implementation, and develop implementation strategies to be included in the framework of CL policy.

In addition to the quantitative approaches used in the previous chapters, in Chapter Eight, the contents of the framework were assessed by qualitative approaches, in order to determine whether it is applicable to the Thai context. This was done by using qualitative data obtained from interview, observation, and literature published by Thai actors. Experiences of implementation of the Thai CL policy were investigated in order to identify key elements that affected the CL decision-making process and implementation in Thailand and analysed to see whether they are consistent with those in the preliminary framework. Any additional elements derived from experiences and insights of CL in Thailand were used to strengthen the framework. Chapter Nine is the conclusion. All elements identified from previous chapters were discussed, and interactions across different elements were analysed, in order to develop strategies to optimise the benefits and minimise negative consequences of implementing CL policy.

Chapter 2: Background to compulsory licensing policy

The inequality between high-income countries (HICs) and low and middle-income countries (LMICs) in access to medicines is an important issue. The UN's Millennium Development Goal 8 mentions the gap in access to medicines as "Prices of essential medicines remain high and availability low, making them unaffordable to large segments of populations in developing countries" [21]. Although the inequality may originate from the difference in ability to pay for drugs and health care services, patent protection of trade interests plays a major role in hindering drug access in LMICs [22, 23]. The WHO has developed a framework in order to guide and coordinate collective action in line with millennium development goal on access to essential medicines. One of the important elements in the framework is CL policy.

The aim of this chapter is to provide background information on CL policy. The background information is classified into four sections: (1) the WHO framework for collective action on improving drug access; (2) the establishment of CL policy, this section provides a history of CL policy established as a remedial flexibility in the TRIPS agreement. The main information was obtained from literature of inter-governmental organisation; (3) the utilisation of CL by LMICs, this section provides broad experiences of CL implementations in LMICs. The main information was obtained from literature of non-governmental organisation; (4) implications of CL in LMICs, this section provides results from a systematic review for empirical evidence on the positive and negative implications of CL policy. The details of each section are provided below.

2.1 The WHO framework for collective actions to improve drug access

The framework for collective action was initiated in line with the millennium development goals. The framework has been adopted by WHO and its partners to improve access to essential drugs. Four factors have been proposed: (1) rational selection and use of essential medicines, (2) sustainable financing, (3) reliable health and supply system, and (4) affordable prices, which could be considered as an alternative to promote drug access [23]. For the affordable prices, the issue can be

pursued through many mechanisms and the TRIPS flexibilities is one of the effective measures to safeguard public health and promote access to medicines. The framework suggests countries should incorporate provisions for TRIPS compatible safeguards such as compulsory licensing and parallel import in to national legislation [23].

Regarding the measures mentioned above, parallel import (PI) is imports of a patented drugs from a nation in which it is already marketed into another nation without the permission of the patent holder. Prices of drug are often different across countries, even it produced by the same manufacturer. The differences in price may be because of local conditions of drug market, such as differences in national IP laws, or national income levels, as well as the degree of drug competition among producers [24]. Therefore, the health care costs could be significantly saved by importing the same drugs from a country where the drugs have a lower price. In addition, voluntary licensing (VL) is where a patent owner offers its licence to a third party (regularly a generic producer) to produce, distribute and sale the patented drug. The use of patent is only permitted if the proposed patent user obtains authorization from the patented owner on reasonable commercial terms. This requirement may, however, be waived by the WTO Member through compulsory licensing (CL). CL is thus a remedy for a variety of condition, including anticompetitive practices; in the case of a national emergency or other circumstances of extreme urgency; and in the case of government use of license for public non-commercial purposes including uses necessary to address public health issues [24]. Therefore, CL is an effective measure recognised by inter-governmental sectors to promote access to essential medicines, and the next section focuses only on the CL measure.

2.2 Establishment of compulsory licensing (CL) policy

The TRIPS agreement has been in force since 1995, and a number of LMICs has applied the CL policy to safeguard public health benefits. [18]. The Agreement sets minimum standards for many forms of intellectual property (IP) regulation as applied to all of the WTO Members. The main aim of the agreement is to strengthen and harmonise certain aspects of intellectual property protection at the global level. However, due to public health concerns, TRIPS also includes provisions, which

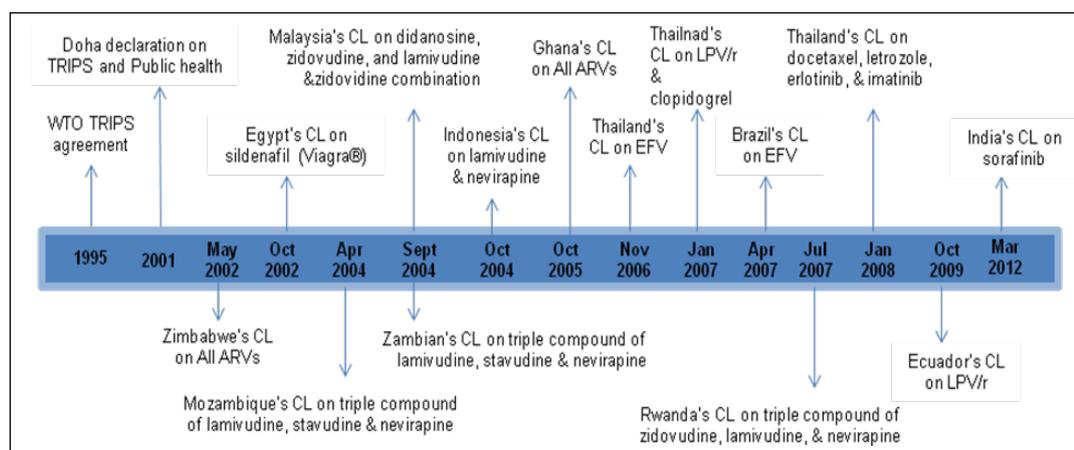
allow a degree of flexibility for the WTO members to safeguard the social benefits of access to medicine. However, LMICs have been reluctant to use these flexibilities because they are unsure of how these would be interpreted, and how far their rights to use them would be respected [24].

In 2001, therefore, the Doha Declaration on the TRIPS Agreement and Public Health affirms and clarifies the right of WTO Members to make full use of the flexibilities of the TRIPS Agreement to protect their public health and improve access to essential medicines [25]. This intended to settle a compromising solution between the principal of public interests in access to essential medicines and the terms of the TRIPS agreement [26]. CL has been affirmed as a solution under the TRIPS flexibilities when the patent protection hinders drug access [23]. In order to take advantage of this CL, patent users must provide notice and pay a royalty to the patent owner. The “reasonable royalty fee” should be paid based on both the particular circumstances of each case, and the economic value of the CL [27]. The practice to determine a reasonable or adequate remuneration is greatly varied, and there is no single accepted method. The Doha Declaration reiterated that countries have "the freedom to determine the grounds upon which such licences are granted" [25].

The IPRs is a tool to increase competitive power of the IP owner’s country over its IP user’s countries. Any actions of the IP users, which seem to infringe IPRs are countered with a strong reaction by the IP owner’s country [28]. The USA is an example, which obviously shows its standpoint on the IPRs issue of pharmaceutical technologies. The Special 301 program of the United States Trade Representative (USTR) is required to yearly publish a list of countries, which “deny adequate and effective protection of intellectual property” or “deny fair and equitable market access for U.S. firms that rely on intellectual property.” That includes the use of CL policy. These requirements resulted in the USTR’s creation of a “Watch List (WL)”, “Priority Watch List (PWL)” and “Priority Foreign Country (PFC)” which serve as warning mechanisms to countries perceived as out of compliance with USTR’s preferences on IP policy. Any country placed on the list could face political or economic sanctions under the Section 301 program [28].

2.3 History of CL policy in low and middle-income countries (LMICs)

According to Beall *et al*, CL episodes from 11 LMICs have been adopted between 1995 and 2010. These were in three continents across the world: South America (Brazil and Ecuador), Africa (Egypt, Zimbabwe, Mozambique, Zambia, Ghana, and Rwanda), and Asia (Malaysia, Indonesia, Thailand and India) [18]. In this section, I explored the CL history by focusing on the 11 countries. Thailand is however not included as this chapter, as it is the focus of the remaining parts of the thesis. The findings are visualised in the timeline in figure 2.1.



Abbreviation: ARVs: Anti-retroviral drugs; CL: Compulsory licensing; EFV: efavirenz; LPV/r: Lopinavir and ritonavir combination; TRIPS: Trade Related Aspects of Intellectual Property Rights; WTO: World Health Organization;

Figure 2. 1 Timeline of CL across the world

Zimbabwe granted CL policy for ARV drugs in 2002. Zimbabwe struggled with the burden of HIV/AIDS. During the early 2000s, each day 564 adults and children became infected with HIV, and the total number of people who lived with HIV/AIDS was between 1.5 and 2.0 million [29]. In May 24th, 2002, P.A. Chinamasa, the Zimbabwean Minister of Justice, made the general notice titled “Declaration of Period of Emergency (HIV/AIDS) Notice 2002” for a six-month-period. This notice enabled the State or an individual authorised by the Minister to produce any patented medicine, including ARVs, and to import any generic drugs to the country [30]. In 2003, the emergency period was extended until 31st December 2008. With the assistance of Indian generic drug firms, a Zimbabwean generic drug company produced generic combivir (AZT/3TC) with at least 50% (US\$15 per

month) lower price than the patented drug (US\$30 per month) [31]. The evidence about the royalty rate has not been found

Egypt is an interesting case as it used CL on Viagra[®]. In October 2002, two months after this drug was approved to be launched into Egypt, the Health Ministry was politically requested by local manufacturers to issue a CL for Viagra[®]. The generic drug was sold at one-twentieth of the Pfizer's Viagra[®] price [32]. However, an argument was raised on the doubtful decision of the Egyptian government about whether this legislation intended to increase access because of public interest [33]. An argument was raised that the public benefit appeared questionable. First, this drug treats erectile dysfunction, which is a health problem, but far from the life-threatening diseases. Second, the Chairman of the Health Committee in Egypt's upper house of Parliament at the time was also the Chairman of a large generic drug manufacturer. Third, the CL decision did not comply with TRIPS because it refused to attempt early compliance with regular processes of the agreement when it had the opportunity to do so. Fourth, the company seeking the CL may have little interest in enhancing access to the drug for poor people in Egypt [34]. After the CL was granted, Egypt got negative reactions from the patent owner and the Pharmaceutical Research and Manufacturers Association of American (PhRMA) in terms of disincentive of investment in Egypt's pharmaceutical sector. In addition, Egypt was placed on the "Priority Watch List/ PWL" by the United States Trade Representative (USTR) [33, 35, 36]. However, among economic sanctions, FDI in Egypt has still increased since 2002 as this growth of investment was dominated by other sections (petroleum industries) [33]. The evidence about the royalty rate and CL period in Egypt has not been found.

Mozambique granted CL policy for ARV drugs in April 2004. Mozambique was ranked as one of the highest nations for HIV epidemic. There were 1.4 million people living with HIV/AIDS in 2004 and 500 people becoming infected every day [37]. On April, 5 2004, Salvador Namburete, the Mozambican Deputy Minister of Industry and Trade decided to issue the CL to a local company Pharco Mozambique Ltd for producing the triple compound of lamivudine, stavudine and nevirapine. Royalties were set at 2% of the total sales [38]. The rationale was made on national emergency grounds, because the international patent holders failed to make the drugs affordable to the majority of the Mozambican people. Moreover, the three

different international owners failed to reach an agreement to produce the drug combination [39]. The triple compound drug was produced with the names of PHARCOVIR 30[®] and PHARCOVIR 40[®] by local generic drug manufacturers.

Zambia granted CL policy for ARV drugs in September 2004. Zambia met the top ten countries in Africa having the high rates of morbidity and mortality from HIV/AIDS. The Ministry of Health estimated that, at the end of 2004, one million adults and children were living with HIV/AIDS [40]. On 21 September 2004, Dipack K Patel, the Zambian Minister of Commerce Trade and Industry issued CL on the triple fixed-dose combination of lamivudine, stavudine and nevirapine to a local company Pharco Ltd with royalties set at 2.5% of the total sales [41]. The application was made based on maintaining and securing sufficient supplies and services essential to the wellbeing of the community. The triple fixed-dose combination was produced with the names of NORMAVIR 30[®] and NORMAVIR 40[®] [42, 43].

Malaysia granted the policy for ARV drugs at the same time as Zambia. In Malaysia, the number of HIV/AIDS cases continued to grow from 38,044 cases in 2000 to 58,012 by 2003. As of September 2004, an aggregate total of 61,486 HIV-infected individuals of whom 8,955 people had AIDS and 7,083 had died, had been reported to Malaysia's Ministry of Health [44]. In September 2004, the Malaysian Minister of Domestic Trade and Consumer Affairs issued a CL to import ARVs, including didanosine, zidovudine and lamivudine and zidovudine combination (Combivir[®]) from the India maker, Cipla [45]. Under the CL, Cipla was allowed to export and sell the drugs to the Malaysian government under fixed ceiling prices for two years [46]. Malaysia set a royalty rate of 4% of the total sales [41]. According to the Malaysian Ministry of Health, the average cost of health care treatment for HIV/AIDS patients decreased 81% after the availability of generic drugs. The expected number of HIV/AIDS patients who could access to the drug in public hospitals and clinics improved from 1,500 to 4,000 patients by using CL, and that encouraged the Ministry of Health to step up the achievement to cover 10,000 patients [47]. Moreover, due to the generic versions available, the patent owners significantly dropped their own prices in the market [47].

A month later, in October 2004 **Indonesia** granted CL policy for ARV drugs. Because, as of January 2004, only 1,300 patients received the treatment compared to

a total of 15,000 patients in need of ART [48]. Therefore, the government aimed to provide ARVs for 5,000 patients in 2004 and 10,000 patients in 2005. The subsidy of US\$240 per person per year for 4,000 patients was not enough for the price of a triple ARV regimen (zidovudine, lamivudine and nevirapine) at US\$564 per person per year. In October 2004, Indonesia issued CL to produce generic versions of lamivudine and nevirapine. The generic versions were produced by a local firm, PT Kimia Farma [49]. Royalties were set at 0.5% of total sales [41]. Regarding implementation of CL, the Indonesian government estimated that in 2006 about 5,000 HIV/AIDS patients from the total of 10,000 patients in the country received ARV treatment under the CL policy. While only 3.5% of patients had access to ARV in 2003, this has increased to 40% in 2005 [49].

Ghana granted CL policy for ARV drugs in October 2005. In the case of Ghana, 90,000 AIDS cases had been reported, and 400,000 people living with HIV/AIDS was estimated in 2004 [50]. On 26 October 2005, Major Courage E.K. Quashigah, the Ghanaian Minister of Health, notified an emergency and issuance of government used license for HIV/AIDS medicines. Ghana declared an emergency situation with regards to HIV/AIDS. It was declared that the ARV medicines would be issued to treat HIV/AIDS patients without any commercial interest and for government use only [51]. The use of CL aimed to import Indian generic ARVs. It was expected that the Ghanaian budget for ARVs would be reduced from US\$ 495 to US\$ 235 for one-year treatment per patient (approximately 50% reduction) [31].

Brazil granted CL policy for ARV drugs in April 2007. Brazil is widely known as a leading country making an impressive battle to overcome the HIV/AIDS problem. However, its attempt was aggressively undermined by the TRIPS agreement. After Brazil passed its revisited national patent law to protect drug patent, the price of ARVs increased by patent protection beyond patient affordability [52]. On November 13, 1996, the president of Brazil, Jose Sarney, pronounced the big challenge by proposing Brazilians' universal and free access to ARVs through the National Health System [53]. The model to promote ARVs access included price negotiation with patent owners; and in the case of failure, the CL policy would be taken into consideration. By threatening to use CL policy, Brazil preserved high power to negotiate with transnational drugs companies and mostly achieved the best price of drugs to pursue its universal access to ARVs [54]. On April 25, 2007, the

Minister of Health, Jose Gomes Temporao, endorsed Decree 866 to notify CL on Efavirenz (Stocrin[®]) for public interest purposes for a period of five years [55], with a remuneration to the patent holder of 1.5% of the drug sale [56]. The use of CL by Indian generic drug companies reduced the total price per day by 50%. It was expected to save US\$30 million in 2007 and US\$237 million during 2007 to 2012 (when the patent of efavirenz expired) [57].

Rwanda granted CL policy for ARV drugs in July 2007, as the last country, which has issued a CL policy in Africa. By the end of 2007, 150,000 people lived with HIV/AIDS and the adult HIV prevalence was 2.8%. In July 2007, Rwanda declared the need to use CL over two years for public health interests. Apo-TriAvir[®] (a combination of 300 mg Zidovudine, 150 mg Lamivudine and 200 mg Nevirapine) was expected to be imported in 260,000 packs from Apotex, Inc, a drug company in Canada. However, according to the Canadian Patent Act, Apotex had to initially seek a voluntary license from the patent owner, but the request was refused by the transnational drug company. Apotex then produced an application under the Canadian Access to Medicines Regime (CAMR) to export generic version of Apo-TriAvir[®] to Rwanda. CAMR paid a royalty rate of 4% of the value of the contract for the supply of the product [58]. In September 2008, Apotex exported 7 million doses of Apo-TriAvir to Rwanda under the Canadian regime [59].

Ecuador granted CL policy for ARV drugs in October 2009. In Ecuador in 2008, 26,000 people lived with HIV and 1,200 people had died from AIDS [60]. Due to the price of drugs, only an estimated 42% of Ecuadorians requiring ARVs were receiving treatment [61]. In October 2009, the Ecuadorian President, Rafael Correa, signed a decree issuing CL for an ARV drug, lopinavir and ritonavir combination (LPV/r). He said that “This is our vision of intellectual property. It’s not a mechanism to enrich the pharmaceutical or agrochemical companies. It’s a mechanism for development for the people.” License requests are considered on a case-by-case basis, depending on their importance to the public interest, including the benefits of reducing costs and increasing access [62]. This decree gave authority to the Indian pharmaceutical industry, Cipla Ltd, to produce the generic version of LPV/r, which was patented by Abbott Laboratories. CL was issued on the ground of public interest. The royalty rate was 4% of the finished product sale [63]. According to its HIV prevalence, the use of CL reduced the national budget by around US\$5.2

million per year because generics were available to the government at US\$800, while the original drugs cost US\$ 1,000 annually per person [64].

India granted its first CL policy in March 2012. Although CL has been done predominantly for HIV/AIDS drugs, India granted CLs on anticancer drugs. In India, a national survey showed that out of pocket spending expenditure on drugs accounted for about 68% of healthcare spending, which is double that in OECD countries (32.8%) in 2009 [65]. India granted a CL on an anticancer drug for renal and hepatic carcinoma treatment, sorafenib (Nexavar[®]), on 12 March 2012 [66]. Natco paid a 6% royalty to Bayer [66]. In granting the CL, the Controller of Patents explicitly declared three criteria that led to the granting of CLs under Indian patent law. First, the reasonable needs of the public had not been met (only 2% of patients in need received Nexavar[®]). Second, Nexavar[®] was available at a price of US\$ 5,610 for a one-month supply, which was considered unaffordable. Third, according to the requirement by the country, Nexavar had not manufactured or granted licence to any local manufacture in India [67]. According to the criteria, a licence was granted to Natco, an Indian generic company with the right to sell sorafenib at 97% less than the price of the patent drug [66].

In summary, the treatment by patented medicines is costly and unaffordable to some governments, especially in LMICs. Often newer medicines are still under patent protection and their prices are higher, compared to older and generic versions. Sometimes the purchase of expensive patented medicines could threaten the sustainability of government-provided health services. In order to address this problem, LMICs decided to apply the TRIPS Agreement to manufacture or import cheaper generic medicines. According to the information mentioned above, positive implications of CL policy were highlighted in terms of considerable cost savings to the budget, while negative sides were political retaliations by the patent owners. However, the policy processes and implications may vary case by case. The next section explores the implications of CL policy.

2.4 Implications of compulsory licensing: a systematic literature review

This section is a systematic literature review that provides empirical evidence concerning the implications of CL policy. While there is a substantial literature on implications of CL policy, most are in an editorial form. This section focuses on original articles using concrete evidence to analyse CL implications. The objective of the literature review was to determine the implications of CL on health, economic and political aspects. The implications referred to positive and negative consequences.

2.4.1 Review methods: 12 databases were searched to cover both published and grey literature. The published journal articles from the area of public health were obtained from Embase (via Ovid Embase Classic and Embase), PubMed, Cochrane library, and Global Health (via Ovid Global Health). Articles in the areas of economics and business were retrieved from HEED (via Wiley Online Library), Econlit (via Ovid), and Business sources premier (via EBSCO). Articles in the areas of politics and social sciences were obtained from IBSS (via Proquest), Social policy and practice (via Ovid), Scopus (via sciverse), and Web of Sciences (via web of knowledge).

The search strategies used controlled vocabulary terms, whenever available, and relevant free text terms, including “compulsory licensing” or “non-voluntary license” or “government use license” in different combinations. According to the first use of CL in 2001, the search period was from 2001 to 12 March 2013. The papers were included in the analysis if they met the eligibility criteria shown in Table 2.1. For data analysis, I categorised information into five sections: publication year, authors, countries of the study, methods of evaluation, and findings of the study. In the findings, I separated the implications found in each study into positive, negative and no causal relationship.

Table 2. 1 Eligibility criteria of the systematic review

Eligibility criteria	Details
1. Type of studies	Original studies that addressed the implications of CL policy. Although some studies used CL as a side issue for their analysis, I considered the results indicating the implication of CL policy. All the statuses of publication (such as Unpublished, In press, or Published) were included. Review articles and editorial papers were excluded from the analysis.
2. Types of intervention	Studies related to the use of CL for public non-commercial use to increase access to health technologies. Papers that did not address the intervention characteristics (such as the use of CL for other technologies, or the use of other public policies to increase access to drugs) were excluded.
3. Types of outcome measure	The outcome of interest was implications of CL policy on health, economic, and social aspects. The studies, which analysed policy process were not considered.

2.4.2 Results: The search strategy gave 1,256 references. After excluding 763 duplicates, 486 papers were screened. 424 references were excluded based on title and abstract because they were not relevant to CL; for example, articles about other kinds of license policies (i.e. driver license, professional licenses) or articles about the use of CL in other technologies besides health (i.e. software and education). Full-text reviews were completed for 62 articles. A total of 52 articles were excluded; 43 review or editorial articles, three policy analysis studies, and six assessed implications of other alternative policies in promoting drug access. Ten studies were included in the analysis (Figure 2.2).

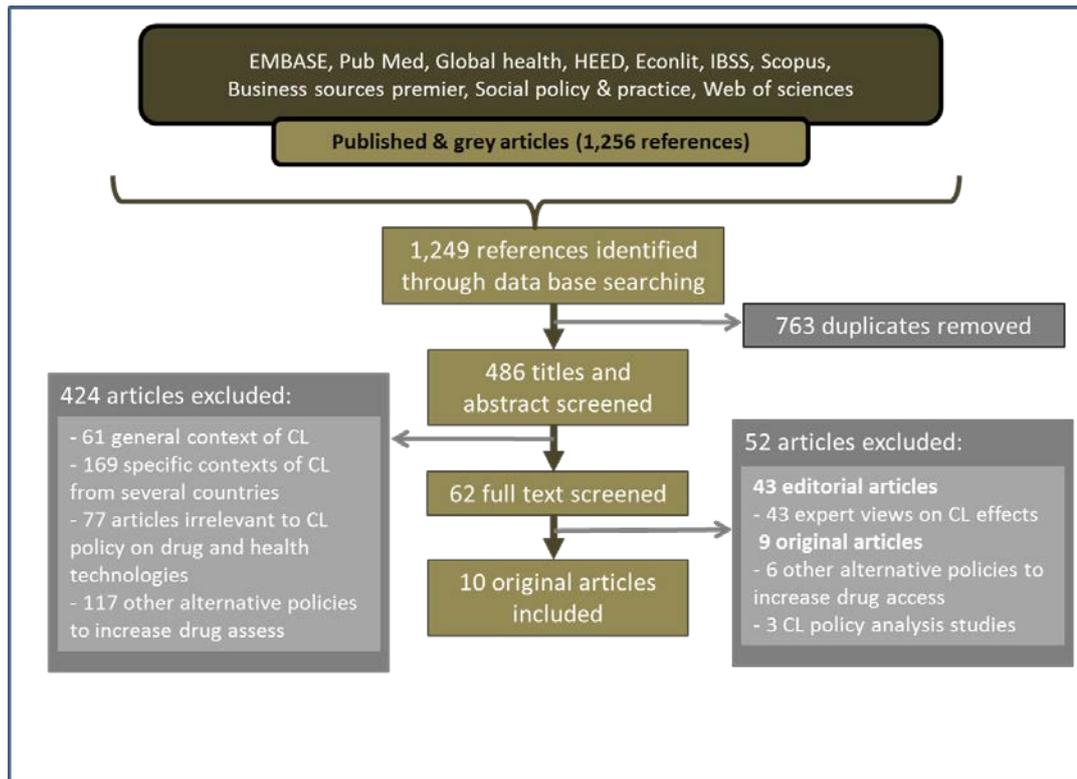


Figure 2. 2 Literature review flowchart

2.4.3 Description of results: Six areas of impacts of CL policy were identified from the ten studies. (1) Three articles indicated impacts of public health benefits created by the government issuing CL policy [68-70]; (2) two articles indicated impacts of economic retaliation by government representing patent owners (e.g. USTR) [70, 71]; (3) two articles indicated impact on drug market in terms of patented price reduction by patented industries [72, 73]; (4) three articles indicated impacts in terms of market competition created by generic drug industries [74-76]; (5) one articles indicated impacts created by patented drug industries on the delay of new drug launches [71]; and (6) one article indicated impacts created by patented industries on drug innovations [77]. Included articles are summarised in Table 2.2.

Table 2. 2 Summary of included articles

Year	Authors	Country	Method of evaluation	Result
1. impacts of public health benefits created by the government issuing CL policy				
2008	Over, M [68]	Thailand	Epidemic & Economic model simulation	Positive impact on the decrease in the national HIV/AIDS treatment budget.

Year	Authors	Country	Method of evaluation	Result
2011	Mohara, A [69]	Thailand	Markov model simulation	Positive impact on the annual national health budget.
2011	Yamabhai, I [70]	Thailand	Human capital approach	Positive impacts on patients' productivity and treatment costs.
2. impacts of economic retaliation by governments representing patent owners (e.g. USTR)				
2011	Yamabhai, I [70]	Thailand	Trend analysis	No causal relationship found between CL and foreign direct investment
2013	Yamabhai, I [71]	Multi-countries	Econometrics model	Insignificant effect of CL on foreign direct investment.
3. impact on drug markets in terms of patented price reduction by patented industries				
2007	Nunn, A [72]	Brazil	Trend analysis	Positive impact on patented price reduction by CL.
2011	Meiners, C [73]	Brazil	Econometrics model	Positive impact on market price reduction by CL and generic competitions.
4. impacts in terms of market competition created by generic drug industries				
2003	Chaudhuri, S [74]	India	Microeconomic model	Positive impact on consumer welfare resulting from the entry of generic firms in the market under CL.
2009	Flynn, S [75]	Not specific	Theoretical analysis	Positive impact on consumer welfare resulting from wealth transferred from monopoly firms to the consumer.
2012	Bond, E [76]	Not specific	Theoretical analysis	Positive impact on global welfare when the technology gap is significant.
5. impacts created by patented drug industries on the delay of new drug launches				
2013	Yamabhai, I [71]	Thailand	Econometrics model	Negative impacts on the speed of new product launches.
6. Impacts created by patented industries on drug innovations				
2002	Chien, C [77]	Multi-countries	Trend analysis	Insignificant decline in drug innovations of patented companies affected by CL

A. Effects on public health benefits

Three studies analysed impacts of CL policy from the government perspective. Two articles analysed intermediate outcomes in terms of national health budget savings from the availability of generic drugs under CL policy. A study by Over (2007) [68] estimated future budget saving for HIV treatment based on the assumption of 90% price reduction by CL policy in Thailand. Another study by Mohara (2012) [69] predicted the size of the budget decrease due to the difference in patent and generic versions of seven medicines according to Thai CL. Although the

two studies used different approaches, both concluded that the grant of CL in Thailand had led to substantial budget savings.

A study by Yamabhai (2011) [70] estimated health implications. The study analysed treatment costs saved and health benefits gained from receiving seven generic medicines under CL policy compared with its alternative treatment being used as the standard treatment prior to the grant of CL. The total treatment cost was calculated from the summation of drug prices and costs of treatment for each drug. This study measured the health benefits in terms of national productivity by using the human capital approach. The increase in national productivity was estimated by multiplying the Gross Domestic Product (GDP) per capita with the estimated Quality Adjusted Life Years (QALYs) gained from the increased drug access. The study found that the use of CL created benefits, which far outweighed its cost.

B. Effects on the national economy

The drawbacks of CL policy were analysed in the study by Yamabhai (2009) [70]. A trend analysis conducted in 2009 comparing before and after CL was issued in Thailand. Because of the reactions from patent industries and the USTR against CL policy, Thailand was placed in the Priority Watch List of annual 'Special 301' report [78]. The study depicted no evidence to support negative effects from CL policy on the changes in investor confidence in not only the stock market investments (both local and foreign investors), but also the foreign direct investments in Thailand. The author re-analysed again in 2013 by using econometric model [71]. The study confirmed that CL does not necessarily discourage foreign investors. Instead, market attractiveness (GDP, population number, and international trade) and political stability are significant factors in attracting foreign investment.

C. Effects on market prices of pharmaceutical products

Studies by Nunn *et al.* (2007) [72] and Meiners *et al.* (2011) [73] evaluated factors influencing the market price of ARVs in Brazil. CL was a side issue in both of these studies. The Nunn study used trend analysis, while Meiners developed an econometric model. Both studies found that Brazil achieved significant discounts from patented drug firms under the threat of CL policy during the price negotiation processes. Moreover, the econometric model indicated that generic drug firms were more likely to respond to factors influencing market competition and demand size,

while patented drug firms tend to strategically set the drug prices to offset CL threats and prices of generic versions available in the market.

D. Effects on welfare of pharmaceutical product consumers

A case study in India by Chaudhuri (2003) [74] used a micro-economic model to estimate price and expenditure elasticity. In the analysis, counterfactual scenarios were assumed that domestic generic drug firms would withdraw from the market by the absence of CL policy. The study found that if CL was inhibited, consumer welfare would decrease because monopoly patented drug industries would dominate the local market. This point was supported by two theoretical studies. Flynn (2009) [75] supported that CL policy allowed generic companies to enter into the market, and subsequently the market drug prices would decrease, thereby transferring wealth from monopoly industries to consumers. Bond (2012) [76] extended the view at global level. It was found that CL policy increased LMICs' welfare; nonetheless, such policy was not always favourable if the effect on the patent-holder was taken into account. It concluded that CL provided benefits to global welfare only when the gap of technology in LMICs and HICs was considerable.

E. Effects on the delay of new drug launches

An empirical study by Yamabhai (2013) indicates that patent protection affected procedure for the launch of new drug products in Thailand. An econometric model of Cox proportional hazard model was employed to examine factors, which determine the entry of new medicines to the Thai market during 1982-2009. The empirical results show that policy related to patent law has a significant and positive impact on the rapidity of the launch of new products in Thailand. Most importantly, CL is shown to have a significant and adverse effect on the speed of new medicine launches. Therefore, the CL caused the delay of new product launches in the Thai pharmaceutical market.

F. Effects on drug innovations

Several arguments have been made that the implementation of CL policy discourages incentives for drug innovations. However, there was only one original study by Chien in 2003 [77], which did a methodological analysis on this issue. The observational analysis compared rates of medical innovation before and after CLs in global. The finding contradicted the perception that there was no measurable decline

in the innovation of license cases under CL. The author postulated that two factors were important on patent companies' decision. This included "predictability" (the degree to which a drug firm could predict that a CL would be used to take a patent) and "importance" (the relative importance of the markets affected by the license). The study concluded that CLs issued on global disease drugs (the drugs that are created for rich countries, but are also useful in developing countries; examples of these are cancer drugs and AIDS therapeutics) were either unpredictable or did not affect important markets at the global level (a wide range of countries which included both rich and poor countries), thereby it found no discernible impact on such innovations. In contrast, CLs issued on neglected disease drugs were predictable and impacted a neglected market for a drug, which would significantly discourage R&D incentives.

2.5 Conclusions and gaps of knowledge

Chapter 2 aimed to set the scene for readers to understand the history and implications of CL policy. According to the study of Beall *et al.* 2012, only few LMICs implemented the CL policy, and the trend of documented CL episodes declined during 1995 and 2010 [18]. A possible explanation is that most countries are concerned about the potential implications, especially political and economic implications, resulting from the policy [19,20]. I conducted a systematic literature review to retrieve empirical evidence on all potential areas of implications of CL policy. According to the systematic review, I found positive and negative consequences resulting from CL policy. This suggested there is value in developing a framework that suggests a comprehensive set of policy elements throughout the CL policy processes and strategies to deal with the potential implications.

In this PhD thesis, I therefore developed a framework for decision making and highlighting implications of drug policy, focusing on CL policy in order to fill the gap of knowledge. I addressed this topic by analysing the case of CL policy in Thailand. The background of the Thai context is explained in the next chapter.

Chapter 3: Background to compulsory licensing in Thailand

The aim of this chapter is to provide background information about CL policy in Thailand. The information was obtained from literature of stakeholders in the public health system such as government, academic, and NGOs in Thailand. This chapter classified background information of Thailand into three sections: (1) the health system in Thailand, this section helps set a scene for readers to understand the context of Thailand; (2) alternative measures for improving access to essential medicines in Thailand, this section provides available measures that used by the Thai government to improve access to medicines in the country, and CL is one of the effective measures; and (3) important events concerning CL policy in Thailand, this section provides a history of Thai CL policy from the beginning of the policy decision until the policy successfully implemented in the country. The details of each section are provided below.

3.1 Health system in Thailand in the context of CL

Thailand introduced CL in 2006; at that time Thailand was a lower-middle-income country with GNI per capita of US\$2,890 and the total population of 65.9 million [79]. The public insurance schemes cover 97% of the population. These are subdivided into: 1) Civil Service Medical Benefits Scheme (CSMBS) for government employees and their dependents; 2) Social Security Scheme (SSS) for private business employees; 3) The Universal Coverage Scheme (UC) as the largest insurance program for any person who is not covered by the other two schemes [80]. The difference across three schemes shows in Table 3.1.

Table 3. 1 The difference across the three public health schemes

Schemes	CSMBS	SSS	UC
Start	1960s	1990s	2001
Target beneficiaries	Government employee, dependents and retirees	Private sectors employees	Thai citizens without the coverage of CSMBS nor SSS
Coverage	8%	14%	78%
Funding	Government budget	Tri-parties (Employee, Employer, and government budget)	Government budget
Payment to health facilities	Fee for services	Capitation	Capitation
Major problem	Constantly raising health care cost	Covering while being employed only	Inadequate budget

Sources: Adapted from the Ministry of Public health's white paper on CL policy [81].

The mission of the Thai ministry of public health (MoPH) is to provide universal access to health care, and medications on the National List of Essential Medicines (NLEM) are provided free of charge. However, there are different aspects across the three schemes. The CSMBS uses the fee-for-service payment by allowing the providers to make almost all health care decisions independently. Therefore, the CSMBS tends to have more access to expensive products outside of the NLEM compared to the two other schemes. On the contrary, the providers under the SSS and UC have a disincentive to utilise expensive drugs since their payment type is capitation. For utilising drugs outside the NLEM, SSS patients have to make a partial payment, while the UC patients have to pay the full price. Therefore, patients under the UC scheme have the most severe problem in drug access and the Thai government have had to find a strategy to solve it [81].

During the last decade, Thailand has faced major health problems from HIV/AIDS, heart disease and cancer. Most of the drugs were patented, expensive, and inaccessible to the middle class and the poor. Some drugs were included in the NLEM but were not fully provided to patients [81, 82]. Due to their prices, which

caused unsustainable public finance, only patients who could not tolerate toxicity of cheaper alternatives would be eligible to use more effective and less toxic drugs [81]. Some were neither included in the NLEM nor covered by the National Health Insurance system; therefore, patients had to pay out of their pocket, and many patients dropped out of treatment when they could not continue to afford the medicines [83]. However, according to the national drug policy, the key imperatives of the Thai pharmaceutical policy is that all eligible Thai people must be able to access essential drugs; and that the Thai health system is sustainable in the long term[84]. The Thai government has tried a number of policies, namely drug patent opposition, drug price regulation and negotiation, and TRIPS flexibilities to promote drug access.

3.2 Policies to promote drug access in Thailand

The Thai government has promulgated measures of patent opposition to promote drug access in the national laws. The Patent Act (No. 3) 1999 (B.E. 2542) supports patent opposition procedures in order to prevent patent applications for medicines that lack novelty (low quality of drug patents) [85]. There are no truly worldwide patents of medicines, and a patent from one country does not offer the inventor any right in another country. Instead, each country or region grants its own geographically limited monopoly for patent protection. The Thai patent office in the Department of Intellectual Property, Ministry of Commerce is responsible for granting patent protection, and the process complies with minimum international standards. However, there is problem called “drug patent evergreening” when brand-name companies make patent applications for medicines that are just little modifications of old medicines. This practice is not looking at any significant therapeutic advantage, but rather a company’s commercial advantage. Therefore, a measure to help in overcoming problems of drug patent evergreening is needed. The patent opposition procedure exists to allow patent offices to examine whether an invention possesses novelty and then to prevent the obstacle of drug access due to the patent evergreening. [86].

Thailand has a pre-grant opposition system to allow any party to oppose a patent application if the application is made for patent protection to a medicine which lacks novelty. The opposition can be made within 90 days after the publication date of the application. If the opposition is denied by the Director-

General of the Department of Intellectual Property, an appeal can be made to the Board of Patents. However, if the Board of Patents also rejects the appeal, the party can be still eligible to appeal the decision of the Board of Patents to the Central Intellectual Property and International Trade Court within 60 days after the Board's decision. If the Court also rejects the appeal, the Intellectual Property and International Trade division of the Thai Supreme Court serves as further recourse. [87]. In the past, the Thai government has rejected the patent applications due to the lack of novelty for Videx® (didanosine /DDI) of Bristol-Myers Squibb (BMS) in 2004; and Combid/ Combivir® of GlaxoSmithKline (GSK) as the combination of lamivudine (3TC) and zidovudine (AZT) in 2006 [88].

In addition to patent opposition, pricing policy is another key measure to control drug prices and promote drug access. The WHO suggests six main methods to control the price of medicines: (1) use of external reference pricing, (2) use of health technology assessment, (3) promotion of the use of generic medicines, (4) application of cost-plus pricing formulae for pharmaceutical price setting, (5) tax exemptions/reductions for pharmaceutical products, and (6) regulation of mark-ups in the pharmaceutical supply and distribution chain [89]. In Thailand, the government has formally implemented the first three policies. Although the other policies have not been implemented yet, concerned actors from academics and NGOs have urged the Thai government to put them into action also. The implementation details of the pricing policies in Thailand and the evidence of the implementation effects are mentioned below.

The Price of Goods and Services Act 1992 (B.E.2542) reflects the issue about price control by enabling the Central Commission on Prices of Goods and Services (CCP) to determine purchase prices or distribution prices of controlled goods, including medicines. However, the regulation was not successfully implemented leading to the variation of drug prices across the country [90], and higher prices compared to other countries [91]. In response to the problems, the Ministry of Public Health and concerned organizations sought to develop a pricing system in the country. In 2015, The Thai government set up a meeting to establish a formal working group among relevant stakeholders from public and private sectors in order to formulate a system to determine a reasonable price for medicines. The

proposed price from the system will be formally approved and regulated by the Central Committee on Prices of Goods and Services [92].

Regarding price negotiation, the government has appointed the price negotiation committee to negotiate the price of medicines with patented industries. The committee employs several tools in the process of drug price negotiation, including price-volume agreement, international price comparison, and value based pricing by using economic evaluation and technology assessment [93]. The price negotiation committee has employed these tools to develop pricing strategies and succeeded in negotiating prices for many medicines. For example, the committee succeeded in negotiating prices of medicines for treatment of hepatitis C by using the measures of value based pricing and volume agreement. The committee also successfully employed the tools to negotiate the price of Peg Interferon and Ribavirin, and achieved 70% reduction from the original prices of the drugs. [94].

In addition, another effective tool is risk-sharing because the approach helps distribute the cost burden between the public payers and the pharmaceutical company. The Thai government also used a risk-sharing agreement through a performance-based reimbursement scheme. The scheme involves the prices of drugs and levels of reimbursement being tied to future performance measures of clinical outcomes related to patient quality and quantity of life. The goal is to offset the risks among health care payers (such as government or insurance companies) of paying huge reimbursement costs for a particular treatment, when there is uncertainty over clinical value and health economic value of the treatment [95]. Drug companies can implement the risk-sharing agreement through offering the treatment with a discounted price, or offering the treatment free of charge within a pre-set timeframe [96].

The MoPH used this risk-sharing approach to promote access to Sunitinib as an anti-cancer drug. HITAP conducted a study to assess a value based risk-sharing scheme for Sunitinib for the treatment of metastatic RCC (Renal Cell Carcinoma). The findings indicated that if the willingness-to-pay threshold was set at 500,000 THB (3 times of GDP per capita) per QALY gained, the drug industry could participate in the risk sharing by offering the treatment free of charge for 16 cycles, or offer the treatment free of charge for 14 cycles and give 20% reduction from the

original price for the rest of the treatment. In addition, when the willingness-to-pay threshold was set at 160,000 THB (1 times of GDP per capita) per QALY gained, the drug industry should offer the treatment with 85% discount for 18 cycles. However, the negotiation between the committee and the patented drug industry did not reach an agreement [96]. Although there was a failure in this attempt, risk sharing could be another tool to promote access to essential medicines at affordable prices. It has however been suggested that this measure requires an effective administration system and strong collaboration between public and private sectors [97].

Lastly, the Thai government has promulgated measures to promote drug access through TRIPS flexibilities. The Patent Act (No. 3) 1999 (B.E. 2542) reflects that the patent protection shall not apply to a number of conditions including the use of TRIPS flexibilities [98]. Two main mechanisms to use patent rights by others than the patent owner have been clarified. First, non-public uses of patent rights are for any individual who wishes to use the patent rights for commercial purposes. This mechanism requires the permission from patent holders. Second, public uses of patent rights are for any ministry or government department who wish to exercise any right for public use by paying a royalty to the patent owner without the requirement for prior negotiation on the permission, on the royalty fees, or the term of patent. This mechanism contains two categories as follows.

(1) According to the Thai Patent Act section 52, “during a state of war or emergency, the Prime Minister, with the approval of the Cabinet, shall have the power to issue an order to exercise any right under any patent necessary for the defence and security of the country by paying a fair remuneration to the patent owner” [85].

(2) According to the Thai Patent Act section 51, “the use for public consumption or vital importance to the defence of the country; or for the preservation or realization of natural resources or the environment; or to prevent or relieve a severe shortage of food, drugs or other consumption items; or for any other public service” [85]. The cases of Thai CLs are issued under this category. However, after failure in trying other alternative measures mentioned earlier, the Thai

government will adopt the CL policy to alleviate the cost barrier of access to unaffordable drugs.

3.3 Issues concerning CL implementation in Thailand

In the production of pharmaceutical products, drug manufacturers have to pass an assessment of standards for pharmaceutical manufacturing according to good manufacturing practice (GMP), as well as other standard requirements of the Thai FDA. This process involves experts from several agencies, including the Thai FDA, the GPO, and the Department of Medical Science (DMSC). These experts visit drug-manufacturing facilities of drug companies that would expect to produce the drugs under CL policy, in order to check the reliability of the production, document and support systems for drug production, and check whether they meet the GMP standard. This was to ensure that drug manufacturing will comply with standards and build trust and confidence among patients, doctors and medical staff in the quality of generic pharmaceutical products [99].

In addition, in Thailand, the implementation of CL policy is integrated into the regular system of drug policy. Before a generic drug is manufactured or imported for sale and use, it must be registered and pre-marketing approved by the Thai FDA. The generic pharmaceutical products must be endorsed by documented evidence showing their therapeutic equivalence to original pharmaceutical products. The bioequivalence study is internationally recognised by the WHO as a method that proves the therapeutic equivalence of drugs. The following factors are considered: the rate and extent of drug absorption into the bloodstream at different time intervals after the pharmaceutical products are provided for humans. These are determined by measuring drug levels in the blood and duration for which they go into the bloodstream among healthy volunteers. This method reveals bioavailability of a generic pharmaceutical product compared with an original drug, which is a reference product. In addition, the firms have to send samples of generic drugs that they produce or import to the DMSC for quality examination, in terms of product identification, uniformity of dosage units, dissolution, and impurities, in order to ensure that their quality meets the national standard for drug regulation [99].

The system was implemented by comprehensively assessing not only the product quality, but also the manufacturing process as the international standard. For

the process of drug approval, the drug suppliers must submit the evidence to the Thai FDA as follows: (1) Application form for drug registration; (2) Drug labels and medication information leaflet in Thai/English; (3) Certificate of free sale, which certifies that the products are allowed to be sold in the producer country; (4) Certificate of GMP, which shows that the drug producers have been granted the certificate for good manufacturing practice; (5) Documents on quality control for drug standards: active and non-active ingredients, production process, details of standard control for raw materials and finished drugs, certificate of analysis for raw materials and finished drugs, and data about the study of drug stability; (6) Published and publicized reference documents showing drug effectiveness and safety; and (7) Bioequivalence study report by institutes or laboratories, whereby such laboratories have international standard certification [99].

Once a generic pharmaceutical product is approved as mentioned above, it can be imported to the country or manufactured for sale and use in Thailand, and the quality of the drugs is then monitored by the government in accordance with the annual post-marketing plan. For the inspection of manufacturing procedure, plant inspections are performed periodically whether they still meet the GMP standard. For the products inspection, the Thai FDA collects product samples and send these to the DMSC and other authorised agencies for testing on whether they still keep to adequate standards by analyzing for fraudulent characteristics or impurities, which have harmful effects to human health. In case of violation, actions like seizure, recall, or confiscation will be executed under the authority of the FDA [100]. In addition, public health personnel, including doctors, pharmacists, nurses and other relevant personnel have to monitor, observe and collect data about undesirable symptoms and unsafe effects from the use of health products, including drugs under the CL policy. The information and reports are sent to the Health Product Vigilance Center (HPVC), the Thai FDA and MOPH for further consideration [100].

Regarding the capacity of regulatory agencies, the limitation in terms of personnel resources and infrastructure is a common issue. In the pre-marketing process, there is a long waiting list of drug approval due to limitation in experts equipped with the knowledge about pharmaceutical sciences and quality assurance. The Thai government has strategic approaches to manage the limitations in order to accelerate the procedure of CL drug approval. Because CL drugs were set as the

national priority, these drugs were prioritized in the approval process before other generic drugs. As a result, the standard procedures for new generic drug registration under CL policy were placed in the priority review, which required 70 days for approval, while other generic drugs required 110 days. This procedure was assured by the Thai FDA and it was fully compliant with the international standard of generic drug approval. [101].

For the capacity of post-marketing inspection, the quality of efavirenz, LPV/r and clopidogrel were approved by the Thai FDA, the DMSC and the GPO. However, infrastructures of central laboratories were not sufficient to meet the national demand of drug inspection. Therefore, the Thai FDA and the DMSC have extended the national capacity of inspection through strengthening capacity of local laboratories in other regions across the country. In addition, Thailand also lacks the capacity to assure the quality of chemotherapy products. To deal with this limitation, the Thai government sends anti-cancer drugs including letrozole and docetaxel to international laboratories for quality assurance [102].

For the drug distribution, budget monies are a key resource for implementing the policy to allow the policy objective and goals to be met. As all Thai people are covered under the three public health benefit schemes: the UC, the SSS, and the CSMBS, the public health budget to provide the essential drugs under national policies is disbursed by the three public health scheme agencies, not paid for by patients' out-of-pocket expenses [103]. Therefore, it can be ensured that all eligible patients can access the CL drugs. In addition, the GPO and NHSO have established the IT system through a Vendor Managed Inventory (VMI) to distribute drugs into the public health system. In the system, government hospitals have to inform the public health scheme agencies about the number of patients entitled to each scheme under their responsibility, and submit an electronic report on administering drug use under CL policy to the agencies every quarter before they receive their disbursement. The three public health schemes provide the hospitals with funds for health services and drugs according to the number of patients, and leave the hospitals to manage the budget on their own [103]. This VMI system helps the GPO to effectively manage stocks in the warehouse and provide drugs to hospitals. By using computer-to-computer communication, the VMI improves the accuracy and speed of data transferred in the drug inventory system. The VMI manage drug

distributions and is responsible for monitoring the use of CL drugs and making sure that the drugs are sufficient to satisfy the requests from users under the three health benefit schemes [103].

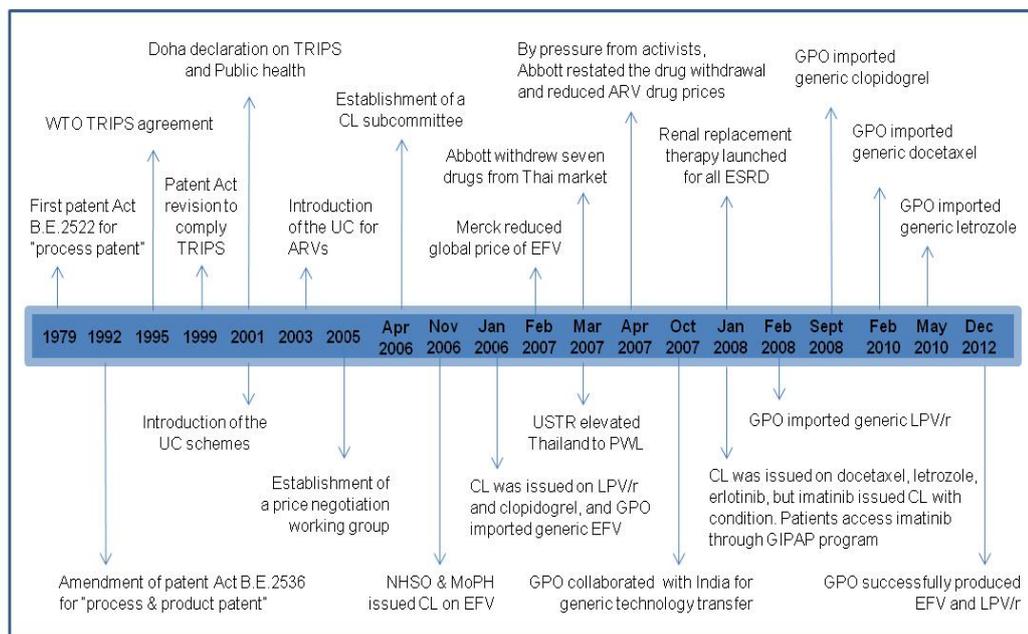
In the step of drug utilisation, under the MOPH's protocol guidelines, the treatment at health care facilities has to comply with the protocol guidelines, and this is followed by an assessment and follow-up of the treatment. In health care facilities, the hospital directors regularly hold meetings with prescribers, in order to discuss specific issues related to their context, to which the main protocol guidelines may not be applicable, and develop their own approaches to deal with the issue [103]. In practice, the doctors examine patients' levels of symptoms and empirical medical data, and judged appropriate drugs for each patient. They are allowed to make changes to use other drugs, which are not included in the MoPH's protocol guidelines. However, the physicians have to submit a written report with attachments, which provide empirical evidence to clarify the reason and need for this change to the hospital director. If any doctors who administered a generic drug and that the drug has no therapeutic efficiency or has any severe adverse effect, they can switch to other generic or patented drugs by submitting a written report to the hospital director [103].

There are two groups of auditors to monitor rational use of drugs: First, the external auditor, which contains authorised government officers from the three public health insurance schemes, randomly audits and monitors performance of drug utilisation in hospital units whether they comply with the protocol guidelines. Second, the internal auditor is authorised local staff of that hospital, who are in charge as a hospital committee for regularly considering and assessing drug administration in their hospital. The committee consists of health personnel with good knowledge of treatment, including doctors, pharmacists, and specialist nurses of that hospital [103].

3.4 Important events concerning CL policy in Thailand

There are several events about the use of CL policy in Thailand, which need to be highlighted. I summarise important events by starting from the first Thai patent act until the successful importation and local production of generic drugs under CL

policy. A history of CL policy in Thailand is visualised in figure 3.1, and explanations on the figure are summarised in the next section.



Abbreviation EFV: efavirenz ESRD: End stage renal disease GIPAP: Glivec International Patient Assistance Program
 GPO: Government Pharmaceutical Organization LPV/r: Lopinavir & ritonavir combination
 PWL: Priority Watch List UC: Universal coverage USTR: United States Trade Representative

Figure 3. 1 Timeline of compulsory licensing (CL) in Thailand

Important events concerning the decision-making processes

In 1979, Thailand introduced Patent Act B.E.2522 as the first legal protection for inventions in the country, which granted exclusive rights to only production process patents for pharmaceuticals [104]. The system provided the opportunity for domestic firms to produce the same product with different manufacturing processes. In February 1992, under pressure of HICs, the “Patent Act B.E. 2535” was amended from the previous patent law to recognise both pharmaceutical products and processes as patentable issues [85]. Since the revised patent act, the Thai medicine market has depended heavily on imported pharmaceutical products. In the 1990s when the new Patent Act went into effect, the proportion of imports rose with accelerating rates. The share of imported drugs in the Thai pharmaceutical market increased from 28% in 1990 to 46% in 2001, and it progressively increased in the following years [105].

In October 2001, the Thai government introduced a Universal Coverage (UC) Scheme of health care insurance from general tax revenue, which covered approximately 47 million people through public and private hospitals. In October 2003, the Thai government also established a universal access to ARV drugs [80]. Evidence shows the considerable increase in a number of patients receiving the ARVs. The enrolment of HIV/AIDS cases from January to December 2003 in the early phase revealed 19,551 patients who were recruited in the program. In the rapid scaling up phase from January to December 2004, the cumulative number of HIV/AIDS patients having access to ARV drugs was 58,133. However, the Thai government bared the burden of health expenditure for medical supplies, which increased from US\$ 1.4 million to US\$ 12 million [82]. In addition, Thailand was faced with treatment costs of other chronic diseases, and measures to reduce the drug prices, therefore, were employed.

In April 2005, Thailand established a working group on negotiating essential drug prices with patented pharmaceutical firms. The members of the working group consisted of representatives from the Ministry of Public health, the Ministry of Commerce, and the Secretary-General of the Food and Drug Administration. By 2006, the working group claimed that the attempt to negotiate the prices of patented drug failed due to lack of cooperation from patent-holders [106]. In April 2006, Thailand's National Health Security Office (NHSO) established a subcommittee to issue CL for government use. The subcommittee developed criteria for using CL on drugs and medical supplies were as follows:

(1) "Drugs listed in the NLEM, or necessary in an emergency or a situation of extreme urgency, or required to solve important public health problems, or needed for prevention and control of outbreaks, epidemics, or pandemics, or necessary to save lives."

And

(2) "Drugs priced too high for the government to afford its citizens with universal access to essential medicines" [81].

There was a political change in Thailand in September 2006. General Surayud Chulanont was appointed to be the interim prime minister of Thailand. Under the provisional government, several policies were introduced, including CL policy for public interests [107]. In November 2006, the Department of Disease

Control and the MoPH issue a government use for CL policy on the ARV drug efavirenz (Stocrin[®]). Thailand continued to issue CL on its other health priorities as follow. In January 2007, the Thai government further issued CL for an ARV combination drug of lopinavir and ritonavir (LPV/r, Kaletra[®]), and a cardiovascular medication, clopidogrel (Plavix[®]). In January 2008, Thailand came to a decision to issue CL for four anti-cancer drugs; docetaxel (Taxotere[®]), erlotinib (Tarceva[®]), letrozole (Femara[®]) and imatinib (Glivec[®]). The royalty fees were paid by generic supplier GPO at 0.5% of their total sale values for efavirenz and LPV/r, and at 3% of their total sale values for the clopidogrel and cancer drugs to the patent owners [81].

The Government Pharmaceutical Organisation (GPO) has been designated to represent the government to procure the seven CL drugs. The GPO aimed to produce three generic drugs, namely efavirenz, LPV/r, clopidogrel. Although knowledge and technology may be initially insufficient to develop the drugs, the GPO improves their capacity through production technology transferred from India generic drug companies. Both ARVs have been successfully transferred the technology. Only LPV/r has been produced, while efavirenz has been decided to import because the prices of Indian generic drugs are cheaper than the local production. For the clopidogrel, the GPO is conducting research and trying to produce it in conjunction with bidding to import from qualified generic drug firms. Nonetheless, the GPO's facilities are not available to produce cancer drugs; so the GPO has to be the agent for procuring the four generic cancer drugs from pharmaceutical companies by considering a certified drug production process and drug quality. The details of each drug are summarised in Table 3.2.

Table 3. 2 The list of drugs granted compulsory licensing (CL) in Thailand

No.	Trade names	Patent owners	Indications	Generic names	Generic firms
1.	Stocrin [®]	Merck	HIV/AIDS	Efavirenz (EFV)	Indian and Thai firms
2.	Kaletra [®]	Abbott	HIV/AIDS	Lopinavir & ritonavir combination (LPV/r)	Indian and Thai firms
3.	Plavix [®]	Bristol-Myers Squib	Cardiovascular disease	Clopidogrel	Indian firms
4.	Femara [®]	Novartis	Breast cancer	Letrozole	Indian firms

No.	Trade names	Patent owners	Indications	Generic names	Generic firms
5.	Taxotere®	Sanofi-Aventis	Lung cancer and breast cancer	Docetaxel	Indian firms
6.	Glivec®	Novartis	Gastrointestinal stromal tumours and chronic myeloid leukaemia	Imatinib	Indian firms
7.	Tarceva®	Roche	Lung cancer	Erlotinib	Indian firms

Important events concerning implementation processes

After the Thai government had decided to issue CL policy **in November 2006**, an announcement was made by Merck concerning the global price reduction for Efavirenz (Stocrin®) to patients living with HIV/AIDS in the least developed countries and countries suffering the burden of the HIV/AIDS pandemics. Merck reduced the price of Efavirenz by 14.5% globally, and the price for Thailand was decreased from 2,000 Baht (US\$62) to 780 Baht (US\$ 24) per bottle. Merck stated that an improved manufacturing process enabled them to pursue their price reduction. Nonetheless, the Efavirenz generic versions remained lower at 650 Baht (US\$ 20) per bottle and Thailand persisted to continue its attempt to increase access to drugs for its citizens through CL policy [81].

In March 2007, the USTR elevated Thailand to its “Special 301” Report Priority Watch List. The USTR cited “In addition to these longstanding concerns with deficient IPR protection in Thailand, in late 2006 and early 2007, there were further indications of a weakening respect for patents, as the Thai Government announced decisions to issue CLs for several patented pharmaceutical products. While the United States acknowledge a country’s ability to issue such licenses in accordance with WTO rules, the lack of transparency and due process exhibited in Thailand represented a serious concern.”[108] Pharmaceutical Research and Manufacturers of America (PhRMA) supported the USTR’s decision to elevate Thailand to the Priority Watch List [109].

At the same time, Abbott Laboratories withdrew seven medicines from drug approval applications to the Thai market and stated that it would not launch new medicines in retaliation on CL for Kaletra®. Those drugs included Aluvia (lopinavir and ritonavir in a new heat-stable form, which required no refrigeration for HIV treatment), Abbotec (clarithromycin in granule of oral suspension for upper and

lower respiratory tract infections), Brufen (ibuprofen in suspension form for fever and pain relief), Clivarine (reviparin sodium for thrombosis, thrombo-embolism, and anti-platelet aggregation), Humura (adalimumab for osteoarthritis, rheumatoid arthritis), Tarka (trandolapril-verapamil combination for idiopathic hypertension), and Zemplar (paricalcitol for hyperparathyroidism in chronic renal disorders) [110].

However, the CL policy was supported by international activists. Over 140 organisations, NGOs and individuals sent letters to the US Secretary of State Condoleezza Rice, and USTR Susan Schwab to require the US government not to interfere with the Thai government decision to subject the CL on the ARV drug [111]. In addition, in January 2007, twenty-two members of the US Congress also sent a letter to Susan Schwab urging her to respect Thailand's decision to issue CL for Efavirenz [106]. Moreover, the practice by Abbott was strongly criticised by treatment advocate groups around the world. Eventually, one month later, in April 2007, Abbott restated such withdrawal from the Thai market and offered to reduce the price of Kaletra by more than 55% for 40 LMICs [110].

The Thai government gained benefits from the CL policy through technology transfer by foreign generic drug producers. The GPO contemplated to pursue a sustainable system for long-term access to essential drugs for Thai citizens. Since **October 2007**, the GPO has made partnerships with Indian drug companies with the aim of improving its ARV manufacturing plant to meet WHO GMP standards [112]. **In December 2012**, the GPO successfully obtained knowledge and technology transferred by Indian industry and produced EFV and LPV/r drug for HIV/AIDS patients, and their quality and safety were approved by the Thai FDA [103]. In addition, clopidogrel is on the pipeline for domestic development. Due to environmental concerns about the cytotoxic chemo substance from anti-cancer production, the plan to produce generic anti-cancer drugs has not been pursued.

As of 2016, five CL drugs have been distributed to Thai patients under the policy. Although Thailand issued CL policy on seven drugs, two cancer drugs were not actually granted. Novartis agreed to provide imatinib for all UC patients under the Glivec[®] International Patient Assistance Program (GIPAP) [83], and the Thai government cannot find a generic version of erlotinib with adequate quality to substitute the patented version. Therefore, CL policy is only implemented in reality for five drugs for three diseases: efavirenz, LPV/r, clopidogrel, docetaxel and

letrozole. These became available in state hospitals in January 2007, February 2008, September 2008, February 2010 and May 2010, respectively.

3.5 The diseases and drugs under CL policy in Thailand

The former government implemented a CL policy in medicines for treatment of three diseases: HIV/AIDS, cardiovascular disease, and cancer. These diseases were selected through need assessment based on national epidemiological data and disease problem projections. The need assessment was conducted by national experts from concerned governmental and academic sectors. The availability and quality of epidemiological data in Thailand is sufficient for public health policy planning. The MoPH has established a disease registry system to support epidemiology, service monitoring, and policy development. Here are examples of methods used to generate epidemiological data on non-communicable and communicable diseases in Thailand.

For non-communicable disease, I give an example of cancers. Cancer registries in Thailand have been working for more than 20 years. The data from five registries of Chiang Mai, Lampang, Khonkaen, Bangkok, and Songkhla were used as the main sources for projection of cancer problems. Statistical modeling of the trend is needed to project cancer problems in the near future. A linear regression model was used when the trend was increasing and a logarithmic regression model was applied when it was a declining trend. Age-standardized incidence rates (ASR) for cancer sites were calculated. Expected cancer cases for each region were calculated based on the age specific incidence rates and the population in each 5-year age group. The incidence rates in Chiang Mai and Lampang were used for estimating expected cancer cases in the northern region. Khonkaen was used to represent the Northeastern region. Bangkok was the representative of the Central region, and the Southern region was represented by Songkhla. All the cases were accumulated to estimate the expected number of cancer cases for the whole Thai Kingdom in future time periods.

Methods to generate epidemiological data for communicable diseases, for example HIV, are more complicated than those for non-communicable ones. The HIV seroprevalence data are reliable in Thailand. However, HIV surveillance in

some target populations (such as MSM and IDUs) is not always available, and information from asymptomatics or those unaware of their HIV status is not always recorded as well. Given the limitations, the epidemiological data can only be determined through the available serosurveillance data in conjunction with other relevant information on levels of risk behaviors, protective behaviors and the magnitude of affected populations. The Asian Epidemic Model (AEM) was used to replicate the transmission dynamics of HIV in Asian settings. Parameters used in the AEM are based on comprehensive reviews, primarily surveys and research studies of population size estimates and behavioral trends: sexual risk behaviors, levels of condom use, injecting risk behaviors, level of sexually transmitted infections. The outputs of that process reasonably match the observed HIV surveillance trends. The AEM was continually used to produce the national HIV projections, for the National AIDS Plan including plan for the CL policy.

A. Rationales for selecting two HIV/AIDS medicines:

Since 2003, the accessibility to ARV drugs among patients has significantly improved when universal access to ARV drugs was implemented [113]. The government increased its national health budget in response to its commitment, but the budget was still insufficient to achieve the goal of universal access for the first line ARVs. In addition, the Department of Disease Control expected that in 2007, there were around 500,000 people living with HIV/AIDS, and at least around 10% (50,000 people) of them would develop drug resistance and require second-line ARVs [81]. If the patients having the drug resistance did not receive second-line ARVs, they would develop opportunistic infections of HIV/AIDS and die. These were deaths happening in the midst of an availability of effective treatments. The proposed expansion of the antiretroviral treatment (ART) program required additional policies to promote drug access, and CL policy was selected to promote the ARV drug access for efavirenz (the first line ARVs) and LPV/r (the second line ARVs).

Efavirenz for treatment HIV/AIDS: Efavirenz is an effective drug for the first line ARV treatment. It is less toxic than nevirapine, which was used as the standard treatment before the grant of CL policy. Nevirapine was locally produced in Thailand within triple based ARV formula with the trade name GPO-VIR®. However, around 20% of patients receiving GPO-VIR® developed adverse drug

events, which sometimes could be life threatening. This raised concerns among healthcare specialists and health policy makers. Empirical evidence revealed that nevirapine could cause serious and life-threatening adverse drug reactions, such as Toxic Epidermal Necrolysis (TEN), Steven Johnson Syndrome (SJS), and severe hepatic toxicity [114-117]. These serious adverse drug reactions affected the patients' quality of life and also increased the costs for treatment of co-morbidity from nevirapine adverse effects. Substitution by a less toxic alternative, such as efavirenz recommended in the treatment regimen, but it was reserved only for patients having a severe adverse drug reaction because of its higher cost [118].

Due to the high price of efavirenz, all new HIV/AIDS patients had to be treated by the more toxic Nevirapine as their first line ARV treatment. Only patients developed severe adverse events; they would be switched to efavirenz of which the price is more than twice of GPO-VIR[®]. In 2006, the Thai Ministry of Public Health (MoPH) granted the CL policy for efavirenz, patented by Merck Sharp & Dohme under the trade name of Stocrin[®]. As a result, there were no need to subject the new HIV/AIDS patients with the more toxic regimen of nevirapine. With the CL, the monthly price of efavirenz dropped from 1,400 Baht (US\$43) to 650 Baht (US\$20) per patient [98]. This allowed more than 20,000 new patients per year to be treated by the efavirenz regimen [81].

Lopinavir and ritonavir combination (LPV/r) for treatment of HIV/AIDS: One of effective second-line ARVs is the Lopinavir and Ritonavir combination (LPV/r), patented by Abbott Laboratories Limited. LPV/r is a Protease Inhibitor (PI), which is commonly used in many countries as a second-line treatment for HIV/AIDS patients who have developed resistance to first-line ARV treatment. A study also found that patients on indinavir and ritonavir combination (IDV/r) were less likely to achieve viral suppression compared to patients on LPV/r [119]. However, due to the high price of LPV/r, it was recommended that patients with first-line drug resistance be treated with the indinavir/ritonavir combination (IDV/r), rather than LPV/r. LPV/r could only be provided to patients who could not tolerate the toxicity of IDV/r [120].

The price of LPV/r was unaffordable by the Thai government to provide the drugs for all patients in need. The monthly cost for the patented LPV/r was 6,000

Baht (US\$186) approximately in 2007, and this meant 72,000 Baht (US\$2,235) per year per patient. The treatment cost required for 50,000 patients would be 3,600 million Baht (US\$112 million). This was more than 100 percent of the health care budget for ARVs treatment in 2007 [81]. The high burden of the second line ARVs costs was the main factor hindering the intention to achieve the universal access to ARV treatment. In 2007, the Thai government were able to support less than 2,000 patients who had developed resistance to the first-line regimen [81]. With the CL, the Thai government expected the price of drug to drop at least to 20% of the current price, which would allow the government to save more than 8,000 lives [98].

B. Rationales for selecting one cardiovascular medicine

Cardiovascular disease can be classified into several types of sub-diseases: cerebrovascular event (stroke), and ischemic heart event (angina and myocardial infarction). In East Asian, stroke causes more deaths than other subtypes of cardiovascular diseases [121]. According to the Thai Ministry of Public Health, more than 50,000 people died from stroke annually [122]. Stroke claimed approximately 50,000 lives annually. In addition, it was estimated that there were more than 250,000 new cases of stroke recorded each year [123].

Clopidogrel for preventing cardiovascular event: Clopidogrel is an antiplatelet drug in the Thienopyridine drug group. It can be used as an alternative, or in addition, to aspirin for secondary prevention of stroke [124]. It has also been found that the use of clopidogrel for secondary prevention in cerebrovascular patients could reduce the death rate of stroke compared to aspirin [124]. The National Health Security Office found that the high cost of clopidogrel was an obstacle to access to this drug, as only the patients who could afford to purchase this drug out-of-pocket or those under the Civil Servant Medical Benefit Scheme (CSMBS), could have access to clopidogrel [81]. Therefore, the Thai government has granted CL policy for clopidogrel, patented by Sanofi Synthelabo under the trade name of Plavix[®]. Due to the CL implementation, the price of generic drugs was 7 Baht (US\$0.2), while that of patented drug was 70 Baht, representing a price differential of 10 times [98].

C. Rationales for selecting two anti-cancer medicines

Cancer disease is one of the top life-threatening diseases in Thailand for over a decade. There were more than 30,000 deaths annually, and more than 100,000 new cancer cases each year [83]. Therefore, cancer was no less serious than the HIV/AIDS and cardiovascular disease. The leading types of cancer in Thailand are lung and breast cancer. There are many new chemotherapeutic and targeted therapies that have been developed in the last decade. Most of the patented new anti-cancer drugs were unaffordable by the government [83]. Many of these drugs, therefore, were not covered by the National Health Insurance system. Patients had to pay their expenses out of pocket. Some of them have to stop taking the drugs because catastrophic illnesses caused bankrupt their family [83].

Letrozole for treatment breast cancer: Letrozole is a hormone therapy drug, which inhibits the production of estrogen that is required for the growth of breast cancer cells. The drug is used for the treatment of early or advance stage of breast cancer that is hormone receptor-positive, or unknown receptor status in postmenopausal women. A study of health benefits of letrozole as the first-line hormone therapy for breast cancer compared to tamoxifen reported higher health benefits in patients receiving letrozole [125]. The Thai government issued CL policy on letrozole, patented by Novartis under the trade name of Femara[®]. The price of 2.5 mg tablet of the patented version was 230 Baht (US\$7), while that of the generic versions were 6-7 Baht (US\$0.2), representing a difference in price at 30 times [98].

Docetaxel for treatment of lung cancer: Docetaxel is a chemotherapy drug used for the treatment of several types of cancers such as breast, lung, gastric and prostate cancers. Among several indications of treatment by docetaxel, lung cancer has the highest number of patients compared to other types of cancers. For the lung cancer treatment, docetaxel is recommended for the stage IV non-small cell lung cancer (NSCLC), including Stage IIIB NSCLC with malignant pleural effusion and/or malignant pericardial effusion with performance status of 0 or 1 with recurrent or relapse after platinum-based chemotherapy. The Thai government has granted CL policy for docetaxel, patented by Sanofi-Aventis under the trade name of Taxotere[®]. Under the CL policy, the price of 80 mg injection is 25,000 Baht (US\$

776) for Taxotere[®], while the generic equivalents cost 4,000 Baht, (US\$124) representing a price differential of 6 times [98].

3.6 Conclusions

This study focuses on the CL policy in Thailand. Because the CL policy has been implemented to improve access to essential drugs for treatment of communicable (HIV/AIDS) as well as non-communicable diseases (cardiovascular disease and cancer), Thailand is the only LMIC which has implemented the policy for a wide range of medicines. In addition, because the former government decided to issue the CL policy in 2006 and the policy is still actively implemented in the country, the eight-year CL experience is sufficiently long to analyse the policy performance and draw concrete insights for decision making and implementation of drug policy, focusing on CL policy. Therefore, the policy insights derived from the experiences of the Thai former government were used to develop and strengthen the framework.

Chapter 4: Study methods

4.1 Overview of methods

This section gives an overview of the research methodologies. As mentioned in Chapter 1, the aim of this study is to develop a framework to aid decision-making and implementation of drug policy, focusing on CL policy. This study is not a policy process analysis, but focuses on specific elements, which are essential to the policy framework. There are four objectives to achieve the overall aim. For objective 1, a framework for decision-making and implementation was developed. The findings from objective 1 were strengthened by insights from experiences of CL in Thailand in subsequent objectives. In objective 2, comparative cost savings were estimated across different types of drugs. The findings were used to help identify key parameters to incorporate into the criteria for drug selection within the decision-making process. In objective 3, the performance of the Thai government on drug procurement, substitution of generic drugs for patented versions, and drug access improvements were evaluated over the eight years of CL policy. The findings from this evaluation were used to help identify strategies for improving policy performance during the implementation process. In objective 4, an analysis of the applicability of the framework in the Thai context was undertaken through stakeholder interviews, document analyses, and observations. Figure 4.1 presents links between the four thesis objectives.

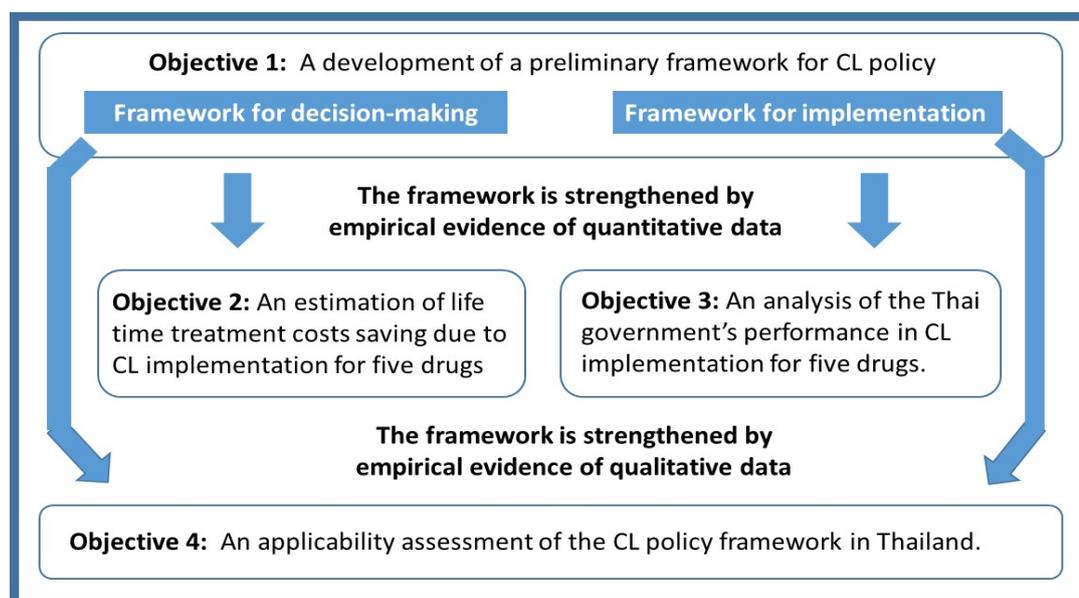


Figure 4. 1 Conceptual framework

Objective 1: To develop a preliminary framework for CL policy

Data collection: Information from the literature was used to develop a preliminary framework to guide the decision-making and implementation of drug policy, focusing on CL policy. A document review was conducted to identify key elements affecting the CL policy process. Several sources of information, including official documents, guidelines and handbooks published by inter-governmental organisations (the WTO, WHO and partners) were included. Such documents were included because they contain generic policy elements and recommendations, which can be commonly applied in any country.

Data analysis: A well-known analytical model, the policy triangle developed by Walt and Gilson (1994), was initially used to guide the identification of policy elements and conceptualisation of the framework. This model was selected because it has been commonly used to study policy in the context of LMICs [126]. The policy triangle model presents a greatly simplified approach to explore a complex set of inter-relationships among four elements; policy content, context, actors and process [127]. Policy content refers to the substance of policy: what the policy aims to achieve, and the conditions required to implement the policy process. Actors refer to the stakeholders involved in the policy. Context refers to the factors, which influence the process of decision making and implementation. Process refers to the stages associated with developing and implementing policy and also interactions between them [128]. I analysed relevant documents to identify the key elements in the CL policy process and the role each element played in the process.

Objective 2: To estimate lifetime treatment costs savings

Data collection: Secondary data were used to analyse implications of deciding to issue CL policy for different types of drugs. The implications were evaluated in terms of comparative lifetime treatment costs for patients receiving the five CL drug compared with the comparator recommended by Thai clinical practice guidelines (CPGs). Secondary data parameters used to estimate the lifetime treatment costs were comparative treatment effects and health care costs. Treatment effect parameters were obtained from published clinical studies or meta-analysis literature where available. Treatment costs consisted of drug costs and health care

services costs for the treatment of HIV/AIDS, cardiovascular disease, and cancer and related complications. Costs of drugs were estimated from the mean drug price per dose multiplied by the mean daily dose per person as recommended by the Thai CPGs. Other treatment costs (disease complications and adverse drug effects) were retrieved from cost studies in Thailand. As mentioned in Chapter 3, although the Thai government announced seven drugs to be included under CL policy, the policy was only implemented for five drugs (efavirenz, LPV/r, clopidogrel, letrozole and docetaxel). Therefore, I analysed the lifetime cost savings only for the five medicines in question. The timeframe of analysis was a patients' lifetime after receiving the drug under CL policy.

Data analysis: State transition ("Markov") models were constructed to calculate the lifetime costs of patients using such drugs. The Markov model was employed because it can reflect the continuing risk of disease progression as the common characteristic of many chronic conditions [129] including HIV/AIDS, cardiovascular disease and cancer. For each of the CL drugs, I used factual and counter-factual scenarios to evaluate policy implications [130]. I compared two treatment options suggested in the Thai CPGs before CL (using alternative treatments prior to CL as counter-factual of without CL scenarios) and after CL (using CL drugs as factual scenarios). The individual lifetime cost saving (at the average age of patients in each disease) was multiplied by the total number of patients who accessed the drugs in order to estimate the cost saving. Identifying total cost savings by comparing different types of drugs helped identify parameters to guide the selection of the most beneficial drug. This policy insight could develop a decision-making framework and drug selection criteria for CL policy.

Objective 3: To analyse performance of the Thai government

Data collection: Retrospective data were used to analyse the performance of authorised agencies in implementing Thai CL policy. In the analysis, performance was classified into three sections; drug procurement, drug substitution, and drug access. All data were obtained from government agencies: the Government Pharmaceutical Organization (GPO) as the main procurement agency under CL; the Health Insurance Systems Research Office (HISRO) as the research institute which monitors CSMBS scheme; the National Health Security Office (NHSO) of UC scheme and Social Security Office (SSO) of SSS scheme. For the same reason as the

previous objective, this objective analyses data for the five medicines actually licensed under CL (efavirenz, LPV/r, clopidogrel, letrozole and docetaxel) in order to evaluate the Thai government performance in implementing CL. The timeframe of the analysis was eight years of policy implementation from implementation (in 2007) until 2014.

Data analysis: The policy implications were evaluated by using factual and counter-factual scenarios [130]. Policy performance was evaluated in terms of an achievement in the three implementation areas of CL policy. Where policy objectives were not achieved, I evaluated the implications of such defective performance or unanticipated results by comparing actual performance (as factual scenarios) with full performance (as counter-factual scenarios). First, the Thai government's performance in drug procurement was analysed: (i) whether there was a sufficient supply of generic drugs under CL policy to meet the national demand, and (ii) the implications of an incomplete supply of a drug occurred, where this occurred. Second, I analysed the Thai government's performance in promoting generic drug substitution: (i) whether patented drugs were fully substituted by its generic version, and (ii) the implications of incomplete substitution, where this occurred. Third, I analysed the Thai government's performance in promoting drug access among patients: (i) whether the numbers of patients who had access to the drugs reached prior expectations; (ii) the implications of incomplete access where this occurred. The findings were useful to identify the magnitude of implications from defective performance or unanticipated results and prioritise areas of policy implementation to be improved in cases of CL. These insights were employed to strengthen the content of the CL policy framework.

Objective 4: To assess applicability of the framework in Thailand

Data collection: Document analysis, semi-structured interviews, and observations were conducted to assess the applicability of the framework in Thailand. For semi-structured interviews, five groups of Thai stakeholders were interviewed: (i) government sectors, (ii) academics, (iii) non-profit organisations (NGOs), (iv) the private sector and (v) health care professionals. Interview respondents were purposely selected according to their roles within the CL policy decision and implementation process. Stakeholders were identified from a

combination of secondary sources (e.g. meeting reports), and a snowball approach. Using the snowball technique, preliminary interviews with stakeholders helped to identify further key informants for inclusion. I continued to collect data until I was confident that all relevant contacts had been interviewed. New interviewees were included in the sample until nothing new was being generated or the information came to the point called 'saturation'. The interviews took 30 minutes for each informant and were held between September 2014 and March 2015. During the fieldwork, I observed four meetings concerning the topic of access to essential medicines in Thailand. The observations were conducted between September 2014 and July 2015, using observational guides. For this objective, qualitative data was obtained for all seven medicines (not the eventual five medicines as in objectives 2 and 3), because qualitative information on all medicines is beneficial in generating lessons learnt for identifying policy elements.

Data analysis: Applicability was assessed in terms of the consistency between the initial framework developed in objective 1 and practical matters obtained from the real case of Thai CLs. The interviews were conducted and analysed in Thai language. The information was coded in order to sort data and generate inputs for the thematic analysis process. The codes were annotated by a respondent number and their affiliations to government sectors (GS), academics (AS), NGOs (NS), private sectors (PS), and health professionals (HS). Information under the codes was analysed by searching for patterns of relationship and seeking explanations for these factors within the data. Information obtained from the informants was analysed to gain insights into key elements that lead CL into policy decision and implementation.

4.2 Quality control of research

Mixed methods, which integrate quantitative and qualitative approaches, were employed in this study. The purpose was to extend understanding of the quantitative and qualitative matters of the key elements in the framework, as well as to strengthen the findings and recommendations [131] [132]. In the quantitative parts, I validated the findings by comparing with previous studies and/or verified the results in expert panel meetings. In the qualitative parts, a triangulation approach was used in order to

enhance the quality and credibility of findings, by comparing information obtained from various document sources and interviews. Moreover, I combined findings obtained from various methods of these three objectives in order to broaden and deepen understanding and the study conclusions. When results generated from different sources and methods converged and agreed it enhanced the quality of findings and interpretations. When results were not consistent, I explored further to understand the reason for the inconsistencies.

I adopted other common approaches to improve the quality of investigation [133]. The study quality was controlled by: considering the validity and reliability of data sources, key informants and documents; illustrating methods of data collection and analysis; and incorporating a wide range of different perspectives. In addition, I embedded verification mechanisms such as expert panel meetings and stakeholder consultations. The study findings were presented through a series of stakeholder meetings: three domestic meetings and one international conference, with the aim of validating findings with views from different stakeholders, including decision-makers, policy elites, academics, NGOs, health professionals and representatives from patient groups.

4.3 Ethical considerations

Key informants participated in this study on a voluntary basis. I sent them an invitation letter with the information on the aims, objectives, methods and expected benefits of the research, as well as the outline of interview questions in advance. Those who agreed to take part were informed about their rights to refuse to answer any particular questions or to leave the study at any time. Every interviewee was asked to sign a consent form before the interview started. The thesis received ethics approval from Thailand's Ministry of Public Health on 13th August 2014 and the London School and Tropical Medicine's Ethics Committee on 8th September 2014.

Chapter 5: A preliminary framework to aid decision-making and implementation of drug policy, focusing on CL policy.

5.1 Introduction

Based on the literature review in Chapter 2, few LMICs have made use of CL policy. One possible explanation is that policy makers in many LMICs are concerned about negative consequences resulting from the policy, and are uncertain about effective strategies to avoid these. There is value in developing a framework for CL policy. This framework should suggest elements and strategies that could be beneficial to LMIC policymakers who expect to use CL in the future. In this thesis, an initial framework was developed by conducting a review of literature published by inter-governmental organisations to obtain a set of common elements affecting the CL policy process. The identified common elements were used as a starting point for developing a framework for CL policy in Thailand. Policy elements indicated in this chapter were strengthened by experiences of Thai CLs in the following chapters.

The objective of this chapter is to develop a preliminary framework to aid decision-making and implementation of drug policy, focusing on CL policy. To develop the preliminary framework, I conducted a literature review in order to obtain the set of common policy elements affecting the process of decision-making and implementation of the policy. Literature such as standard practices, guidelines and policy documents, was primarily obtained from site resources of the World Trade Organization (WTO) and the World Health Organization (WHO). In addition, an analytical model for analysing public health policy was employed as guidance for classifying and conceptualising policy elements in a systematic way, in order to create a preliminary framework of CL policy. The details of review and the policy analysis model used for guiding the development of CL policy are mentioned below.

5.2 Scope of the review

A literature review was conducted with the aim of identifying key elements affecting CL policy processes. Using the site resources of the WHO and WTO, the search terms were “compulsory licensing” or “non-voluntary license” or “government use license” in different combinations. The document review included only literature from International organizations (the WHO and WTO) and excluded studies from NGOs and academic research. The reason was that literature of NGOs and academics provided recommendations which were specific to a certain group of countries or interests, while the literature from the WHO and WTO contained general recommendations, which took into account the circumstances of a wide range of countries. In addition, the main objective of literature from the inter-governmental organizations is to advise countries. Therefore, the recommendations or advisories from these organizations were suitably helpful to be employed for developing the preliminary framework. The search period was from 1995 (the introduction of TRIPS) to 30 October 2015. Literature was included in the analysis when it met the inclusion criteria as follows: official policy articles, standard practices or guidelines, published by inter-governmental organisations, or highlighted issues reflecting global perspectives on TRIPS agreement on public health and access to medicines.

The database search gave 590 references (Figure 5.1). 531 papers were screened, after excluding 26 non-English articles and 33 duplicates. After title and abstract review, 505 references were excluded because they were news or conference meeting articles; not relevant to policy guidelines, regulation, or standard practices; not relevant to medicine products; published by non-intergovernmental organisations; context-specific literature; or not available in full report. Full-text reviews were completed for 26 references. A total of 18 references were excluded; 8 references were not standard practices or guidelines, but rather technical reports, and 10 references mentioned the TRIPS agreement as a side issue. Therefore, 8 papers were included: 1 papers published by the World Health Organization (WHO), 2 papers published by World Bank, 2 papers published by the United Nations Development Program (UNDP), 1 paper published by

the United Nations Conference on Trade and Development (UNCTAD), and 2 paper published by the South Centre. I summarise findings of literature in table 5.1.

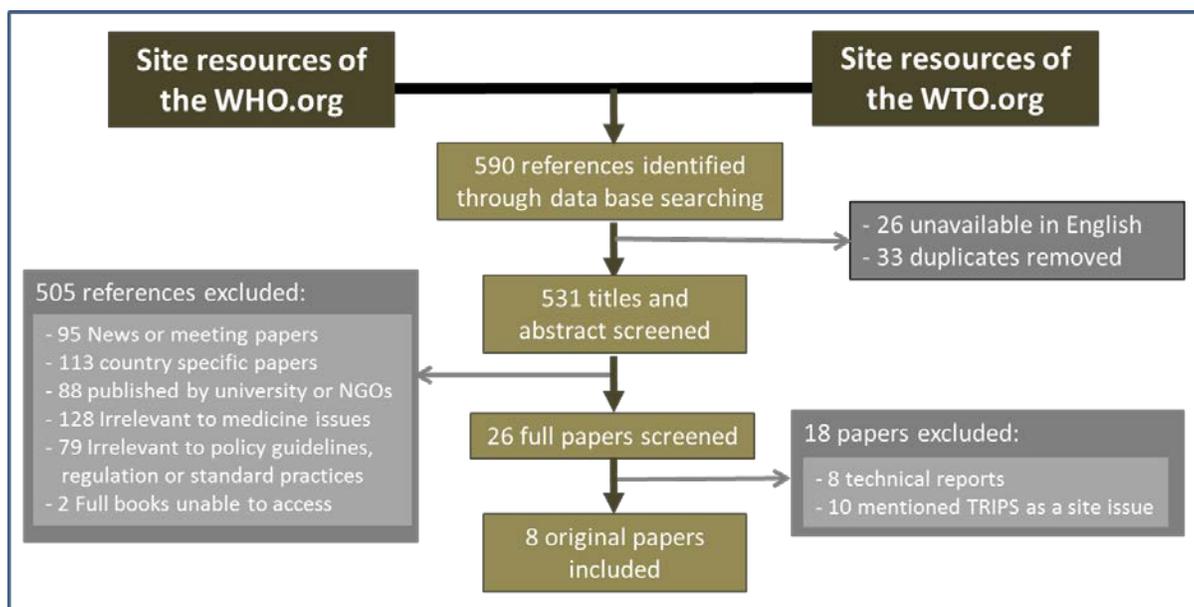


Figure 5. 1 Systematic review flowchart

Table 5.1: List of literature used to develop the preliminary framework

Titles	Contents
<p>1. Title: Good Practice Guide: Improving Access to Treatment by Utilizing Public Health Flexibilities in the WTO TRIPS Agreement.</p>	<p>The guide was published by the United Nations Development Program (UNDP). The guide analyses issues relevant to the TRIPS flexibilities in public health and provides examples where and how they have been used by national governments. In addition, it provides various recommendation of the national practices about how to use the public health flexibilities and mitigate efforts to limit their effect.</p>
<p>2. Title: Compulsory licensing for public health: a guide and model documents for implementation of the Doha Declaration Paragraph 6 Decision.</p>	<p>The paper was published by the World Bank. This paper provides model legal documents to assist countries in implementing the Doha Declaration. This is a convenient starting point for implementation of the Paragraph 6 Decision. The documents include the notification by developing country members to council for TRIPS of intention to use the policy as importer; the notification of importation by least-developed country</p>

Titles	Contents
	member, and developing country member; the notification to right holder of issuance of CL, the model provisions for the legislative or regulatory amendments for exporting and importing countries.
<p>3. Title: Using Intellectual Property Rights to Stimulate Pharmaceutical Production in Developing Countries: A Reference Guide.</p>	<p>The paper was published by the United Nations Conference on Trade and Development (UNCTAD), Division on Investment and Enterprise (DIAE). The guide aims to assist developing countries, and least developed countries. It is an important tool for guiding the countries to establish domestic IP regimes that facilitate increased access to affordable medicines through a variety of policy tools, focusing on the flexibilities provided under the Agreement on TRIPS. The guide is an important tool for training activities for stakeholders, in an effort to build capacities for the creation of domestic legal frameworks conducive to the promotion of drug access.</p>
<p>4. Title: Pharmaceutical innovation, incremental patenting and compulsory licensing.</p>	<p>The paper was published by the South Center. The study covers issues of pharmaceutical patents, including patent proliferation and patentability standards for drug innovation. The study confirmed many available drugs would not be deemed patentable if more rigorous standards of patentability were applied. The application of well-defined patentability standards could help governments avoid granting CL.</p>
<p>5. Title: Remuneration guidelines for non-voluntary use of a patent on medical technologies.</p>	<p>The paper was published by the UNDP. This paper addresses the following issues: WTO provisions regarding remuneration for non-voluntary use of patents; experience of royalty setting in voluntary and non-voluntary settings; the policy framework for setting royalties on medicines in developing countries; and proposed royalty guideline frameworks, which will be desirable for countries to adopt guidelines to enhance transparency and predictability.</p>
<p>6. Title: Battling HIV/AIDS: A Decision Maker's Guide to the Procurement of Medicines and Related Supplies</p>	<p>The paper was published by the World Bank. This Guide on procurement of HIV/AIDS medicines and supplies is meant as a guide for implementing agencies and donors. The guide sets out principles and guidance to ensure that such procurements will fit within an overall well-</p>

Titles	Contents
	functioning supply management system such as product selection, quality assurance, and countries' intellectual property right systems.
7. Title: Regional framework for action on access to essential medicines in the Western Pacific (2011–2016).	The paper was published by the WHO regional office for the Western Pacific. The paper was endorsed by Member States to provide guidance for developing actions to improve access to essential medicines and to strengthen pharmaceutical systems. The Framework for Action provides strategic direction and guidance for WHO collaboration with Member States.
8. Title: Utilizing TRIPS flexibilities for public health protection through South-South regional frameworks.	The paper was published by the South Center. This paper provides strategies for developing countries to overcome national constraints in the use of TRIPS flexibilities. This study provides a conceptual as well as strategic basis as the first step for further thinking and decision-making on how effectively to use TRIPS flexibilities for public health purposes through regional South-South mechanisms and cooperation.

According to the literature summarised in Table 1, I found all documents were beneficial to be used for developing the framework, but some issues were omitted from the literature. The first three papers: the good practice guide published by the UNDP, the model document published by the World Bank, and the reference guide published by UNCTAD, were used as the main references to identify common elements for policy makers to consider procedures to obtain TRIPs flexibilities and develop CL policy. In addition, the paper number four published by the South Center gave recommendations in areas of drug patent, and key issues to be considered before initiating or in parallel to obtaining CL policy. The paper number five published by the UNDP provided guidance to determine adequate and reasonable remuneration of patent use. Although these five papers well addressed policy elements especially in the stage of policy decision, the issues seem to vary across the countries and need to be further explored through empirical research. In addition, relevant issues in the stage of policy implementation,

such as procurement, regulatory system, supply chain management and stakeholder participation, were omitted from the literature.

The last three papers addressed policy elements throughout the process of decision making and implementation. The paper number six published by the World Bank addressed key elements for procurement of medicines and related supplies of HIV/AIDS treatment. However, the paper focused the procurement of health goods to only the HIV/AIDS context. The paper number seven: the WHO's regional framework and the paper number eight: the south center's regional framework, suggested policy elements to promote access to essential medicines in the context of collaboration between the Member States. As both papers are regional frameworks, the recommendations are more practical than other six papers. However, they do not separate actions for countries. In addition, the frameworks pinpointed only issues that were the key problems at the particular time. These papers do not provide a framework of policy action from A to Z until the completion of policy implementation.

In conclusion, it is clear that countries vary enormously with respect to their political and economic situations, legal frameworks, public health systems and drug policy objectives. The authorities of each country have to prepare their own solution that is right for their situation, because the actual implementation will take place within the existing regulatory policy, health system capacity and practice. Therefore, the preliminary framework needs to be further explored and strengthened by information and knowledge derived from experiences of the Thai former government, in order to incorporate practical issues based on the specific context of Thailand.

5.3 Analytical model

The model of the “policy triangle” was used in this study. The purpose of the policy triangle is to help in systematically categorizing and comprehensively listing the elements of concern in CL policy that need to be considered by policy makers[128]. The four sections of the policy triangle are: policy content, context, actors and process. This policy triangle model provides a systematic approach for thinking about elements of the policy process to be included in the CL policy framework [128]. For this study, I made

a framework containing the four sections (Figure 5.2). Details of each section are explained below.

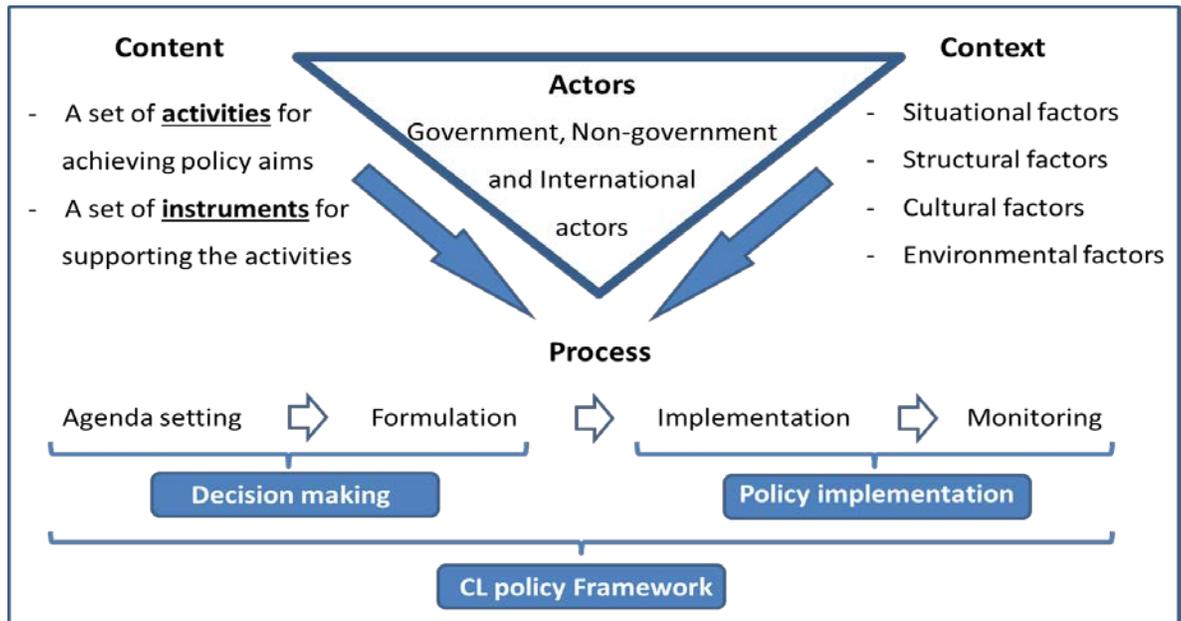


Figure 5. 2 The framework developed from the policy triangle approach

Regarding the four sections, *policy content* refers to substances, which details its component parts, of the policy in question [128]. In this study, **policy content** focused on the policy aims requiring a set of concrete activities and supportive instruments. The supportive instruments included, for instance, policy legislation, operational guidelines, administrative systems, and databases of relevant information. Therefore, in terms of the framework, activities and supportive instruments are components of the policy contents that make it possible to implement a policy.

The *contexts* were classified into four factors affecting the policy process: (i) situational factors, which are transient and impermanent conditions, (ii) structural factors, which are relatively unchangeable elements of society, (iii) cultural factors, the social values of stakeholder groups, and (iv) environmental factors, factors beyond the boundaries of a political domestic system, such as the role of transnational companies and international agreements [134].

As CL is a public policy, relevant *actors* involved in the policy could come from government sectors as well as from for-profit and not-for-profit organisations at national and international levels. Various types of interested groups in the public sector have different roles, resources, capacities and strategies to involve in or influence the policy [128]. In this study, I classified actor/stakeholders into three groups: government, non-government and international actors.

The *policy processes* were divided into four sections: agenda setting, formulation, implementation and monitoring. Agenda setting refers to a stage where public policy problems get the attention of decision-makers, leading to a selection of policies to solve the problem. In the formulation stage, policy elite bodies design and enact the policy. Implementation refers to a stage where governments operate the designed policy in practice; and in the monitoring stage the policy implications are analysed [135]. Policy analysts criticise this conception of the policy process as composed of linear and discrete stages, arguing that this does not reflect reality [136]. However, I decided to use the linear stages because it helped me to clearly situate influencing elements in each of the discrete stages in the policy framework.

5.4 Framework development

According to the framework, there are four stages of the policy process: agenda setting, policy formulation, implementation and monitoring. Each stage contains four elements: contexts, policy contents (activities and supportive instruments), and actors; therefore, sixteen themes were analysed. A deductive approach was used to develop the framework to aid decision-making and implementation of drug policy, focusing on CL policy. The retrieved documents were reviewed, conceptualised and interpreted according to the sixteen themes of analysis. Pieces of information relevant to the defined themes were selected and arranged to link with the framework. Finally, information under particular headings of the thematic topics were narrated as key policy elements in each of the discrete stages of policy process.

The framework for agenda setting and formulation

Results within each process are presented under thematic headings: contexts (C), activities and supportive instruments under each activity (A) and actors or players (P). Figure 5.3 shows the eleven key elements of CL policy process in the stages of agenda setting and policy formulation. Agenda setting is an initial stage in the policy process when a list of issues or problems move an idea onto an agenda, while policy formulation is the next stage when policymakers opt for a particular policy (CL policy) over other alternative measures.

The first stage in policy process is the agenda setting. Six elements were identified, including:

- **One contextual element:** the combination of unmet public health needs due to drug patent barriers and an availability of TRIPS flexibilities (C1.1);
- **Four activities:** identification of unaffordable drugs which are essential for the public health system (A1.1); consideration of patent opposition measures (A1.2); consideration of price negotiation measures (A1.3); and consideration of TRIPS flexibilities (A1.4);
- **One set of actors:** Multi-ministry and patented firms (P1).

The second stage in the policy process is the policy formulation. Five common elements were identified, including:

- **One contextual element:** common interpretation of the TRIPS flexibilities (C2.1);
- **Three activities:** development of CL policy proposal (A2.1); identification of generic drug sources (A2.2); adoption of streamlined procedures to implement the CL policy (A2.3).
 - **One set of actors:** Multi-ministry and patented firms (P2).

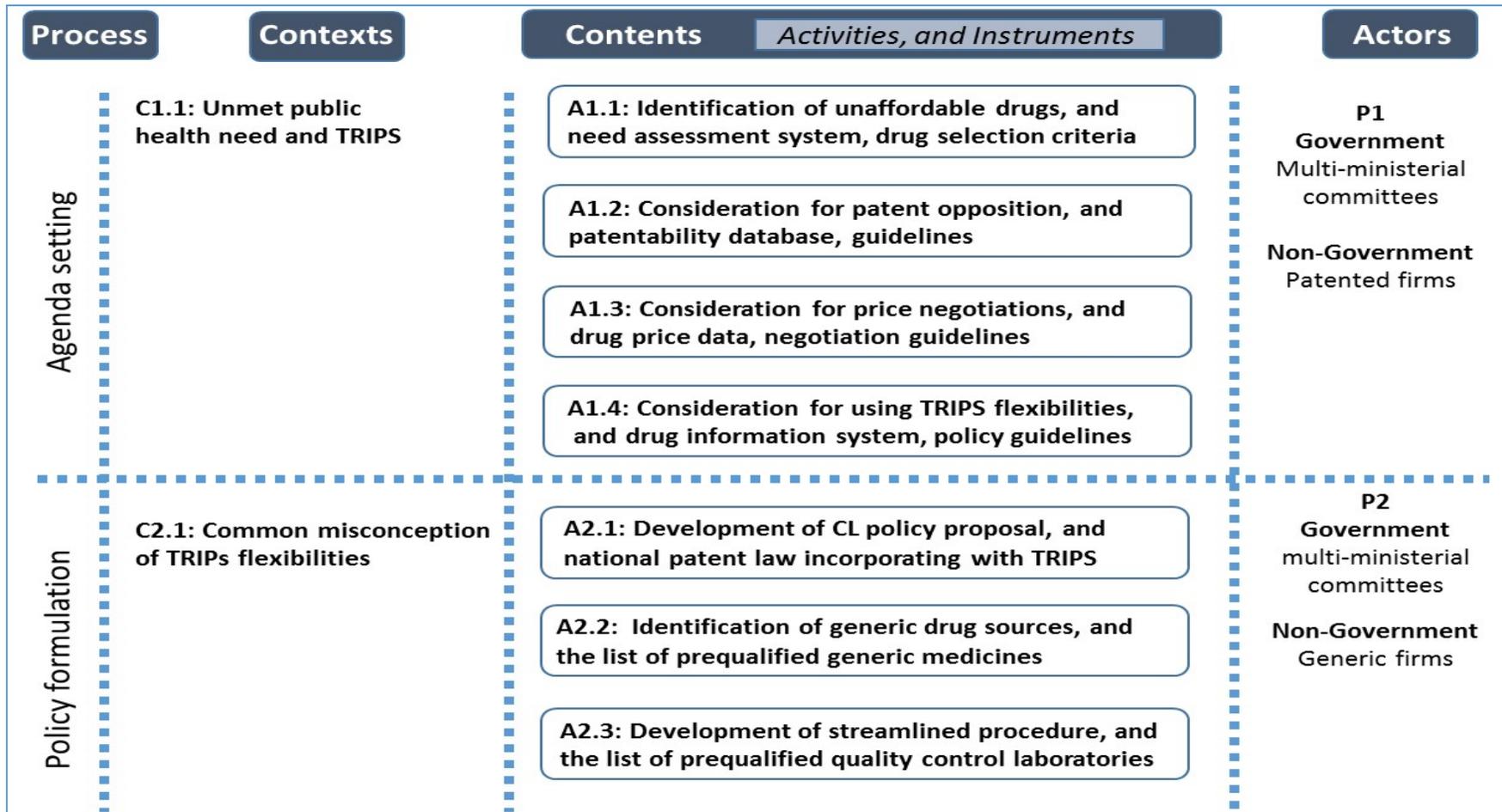


Figure 5. 3 The preliminary framework for agenda setting and policy formulation

5.4.1 Key elements in agenda setting

Context of the agenda setting

The combination of unmet public health needs due to drug patent barriers and an availability of TRIPS flexibilities (C1.1): An unmet public health need due to poor access to patented essential medicines is likely to be the main situational context required for agenda setting. Unmet public health needs can prompt society and governments to address the issue of unaffordable drugs due to drug patent barriers. The growing disease burden leads to a growing need for essential medicines, which in turn requires sufficiently large budgets to meet that need. To meet the increasing need, countries have to ensure efficient and reasonable use of the resources available to the public health system and/or patients [137]. There are several solutions to the problem of unmet public health needs. For example, TRIPS flexibilities are a key policy solution to where patent barriers limit access to essential drugs. The UNDP recommends that countries should adopt a robust set of remedial TRIPS flexibilities if barriers to access to medicines arise [24].

Contents of agenda setting process

Identification of unaffordable drugs (A1.1): The first activity required at this stage is to identify areas of unmet public health need. It is suggested that transparent processes and evidence-based methodologies are required to identify areas of public health need and to select essential but unaffordable drugs [137]. According to WHO recommendations, many essential factors are considered, such as the prevalence of disease, demographic patterns, health care facilities, experiences of local staff, financial resources, and environmental factors. The WHO Expert Committee on the Selection and Use of Essential Medicines prefers drugs that have adequate and concrete evidence on safety and efficacy in using a diversity of health care settings [138]. However, the decision-making becomes more complex when unaffordable medicines are needed.

Key elements to support this activity: there are additional instruments, which are required to identify and prioritise unaffordable drugs. Supportive instruments for identifying unaffordable but essential drugs include *need assessment systems* for identifying type and quantity of drugs that are required [139]. Important variables to quantify and prioritise needs include the size of the affected population, the social and economic consequences of the disease, and the financial resources required to meet the need [140]. There should be an accurate and transparent system for identifying unaffordable drugs. This is because underestimates may deprive some patients of treatments. Overestimations may waste budgets and resources, for example if unused drugs expire, or diagnostic and treatment protocols change [140]. Therefore, careful judgement is necessary, and common methods have been published elsewhere [141, 142]. Quantified needs could be prioritized by predetermined criteria developed from any existing guidelines of national drug programs and expertise, in order to achieve the best drug selection for national public health needs [140].

After identifying unaffordable drugs, policy makers need to consider strategies to overcome patent barriers to these medicines. There are several alternatives, which WTO country members may use to promote drug access such as patent opposition, price negotiation, and TRIPS flexibilities. Patent oppositions should resolve problems where drugs are unaffordable due to patent barriers. This measure can exclude unqualified patents of pharmaceuticals from obtaining the patent protection that prevents more affordable generic versions of the drugs to come onto the market. Second, the government or authorised sectors may negotiate on price, if the drugs are protected by a verified patent, in order to obtain a more affordable price. Finally, TRIPS flexibilities are an alternative measure to consider because they also indicated as one of the key measures to secure access to affordable drugs. Measures to overcome patent barriers to access to pharmaceutical products are highlighted below as the next step for policymakers [24, 137, 140].

Consideration for patent opposition (A1.2): Depending on contents in a national body of law, an invention is legally patentable if it meets the predetermined legal conditions to be granted a patent protection. Countries should use rigorous

methods to assess the novelty and inventiveness of drug's patent applications in order to ensure an acceptable quality and validity of drug patents and also diminish frivolous patents (such as patents on secondary features, different uses or therapeutic approaches of the same pharmaceutical substances) [143]. A verification of patent validity can be made through a pending patent application (called pre-grant opposition), or a granted patent (called post-grant opposition) [24]. This approach plays an important role in screening a particular drug before granting a patent. Authorised agencies should consider the patent status of unaffordable drugs, which are associated with an unmet public health need. If the drugs are not under patent protection, generic versions can be launched to promote competition and reduce the market price. However, if the drugs are in the process of patent application or already protected by a patent, a verification of the drug's patent validity through pre-grant or post-grant opposition, respectively, should be considered [24].

Key elements to support this activity: there are additional instruments, which are required to support the patent opposition of pharmaceutical products. Supportive instruments in this activity are ***patentability database and guidelines***. National laws should include patent opposition as a legal administrative proceeding, which permits third parties to legally oppose or dispute the quality and validity of drug patent [143]. Therefore, it is important to ensure that information pertaining patent-status permits relevant stakeholders to effectively implement patent oppositions and TRIPS flexibilities. However, since patent oppositions in LMICs seem to be hindered by the lack of reliable pharmaceutical information systems [143], countries should pay more attention to developing these. In addition, it is suggested that countries should adopt rigorous criteria for patentability; implement guidelines for patent examination; offer liberal pre- and post-grant opposition proceedings [24]. Standard guidelines to examine patent applications have been developed by ICTSD, UNCTAD, and WHO [144].

Consideration for price negotiations (A1.3): Price negotiation is an effective measure used by procurement agencies to achieve affordable drug prices. It is suggested that countries should develop mechanisms that contribute to price reductions of patented drugs [137]: (1) Bulk purchasing is a direct contracting procurement strategy that

improves the public purchaser's ability to negotiate lower prices depending on the magnitude of the procurement contract; (2) Price comparison is a measure that procurement organizations can use to improve their negotiating power (by collecting information of international drug prices based on prices at similar points in the drug supply chain); (3) Equity pricing is the concept that poor countries should pay less than rich countries in order to make drugs affordable to patients of all country income groups. Patent drug firms may lower their product' price, but gain more sales volume to maintain their total business profits [140].

Key elements to support this activity: there are additional instruments, which are required to support the price negotiation system. Supportive instruments to facilitate authorised agencies in the activity of price negotiation are **drugs price information systems and guidelines for price negotiation**. Effective price negotiation requires an accurate and comprehensive information system, in order to maximise the bargaining power of procurement agencies. Purchasing agencies also require an information system that allows them to assess need and consider appropriate quantities of the drug to respond to that need, thus developing an effective procurement proposal for the bulk purchasing mechanism. In addition, information on the international price of each drug also plays an important role in international price comparison and equity pricing. It is suggested that authorised agencies should exchange information about regional drug prices and promote cross-country comparisons [137]. Collating such information could provide a valid benchmark of the lowest drug prices available worldwide. Several strategies to deal with the price of drugs are already mentioned elsewhere, for example the WHO guideline on country pharmaceutical pricing policies [89].

Consideration for using TRIPS flexibilities (A1.4): TRIPS flexibilities should be another measure to meet the need for particular drugs. TRIPS flexibilities are indicated as one of the key measures to secure access to more affordable medicines [24]. This measure should be applied after the first two approaches mentioned above have been carefully considered, but have been unsuccessful to solve the unmet public health needs. The TRIPS flexibilities include three main measures: parallel imports (PIs), voluntary licensing (VL) and compulsory licensing (CL).

Key elements to support this activity: there are additional instruments, which are required to support the use of TRIPS flexibilities. Supportive instruments for considering TRIPS flexibilities are **policy guidelines and drug information systems**. Policy guidelines under the TRIPS flexibilities have been published elsewhere [24, 145]. This activity also requires a comprehensive information system, including information about patent status and sources of drugs for procurement through PI or CL. If the database is incomplete, the use of TRIPS flexibilities, such as CL, can be uncertain because procurement agencies cannot define sources of generic drugs and the patent status of the drug in question [143]. The main points of each measure are described as follows.

1) **Parallel import (PI)** As mentioned in Chapter 2, PI allows countries to import a patented drug when the product has been marketed anywhere in the world by the patent holder or by another authorised party. The TRIPS Agreement and Doha Declaration acknowledge that nations have the freedom to implement parallel import [24]. However, three points should be borne in mind when PI is considered. First, drug sources are normally limited to PI because drug producers aim to satisfy only the demands of their domestic market. Second, the patent holders may react by increasing drug prices or curtailing drug supply where PI undercuts efforts to promote their local business. Third, some PI may not be directly sold and delivered by drug producers, but by wholesalers or middlemen, leading to potential quality issues. Therefore, drugs procured through PI may require adequate capacity for quality assurance [140, 145].

2) **Voluntary licensing (VL)** is where a person or party uses the license of a patented medicine with the permission of the patent holder. The party must attempt to obtain a voluntary license from the patent owner on reasonable commercial terms and conditions [146]. Therefore, in order to grant VL, there must be an agreement between the patent owner and the patent users; the patent owner may have requirements in exchange for the patent use. For example, the patent owner may impose additional restrictions, such as what price the drug can be sold, where the patent users can sell the drug, and any other terms or conditions that the patent owner can insist on. Therefore,

before granting VL, the exchanges should be carefully considered whether they do not create new barriers to the drug access [147].

3) **Compulsory licensing (CL)** is where a person or party uses the license of any patented medicine without permission of the patent holder. CL can be granted to remedy a variety of anticompetitive practices, to address a national emergency or other circumstances of extreme urgency, or for public non-commercial use (or government use), as mentioned in Chapter 2 [24]. Although common practice requires licensees to first request a VL from the patent owner, certain requirements are waived in order to hasten the process [148, 149]. It is noteworthy that most countries issuing CL policy have been faced with negative political impacts (Chapter 2). Therefore, authorised agencies should consider alternative measures before issuing CL: patent applications should be correctly scrutinised; drug price reduction, parallel import or voluntary licensing should be thoughtfully considered. After other alternative measures, CL policy may be applied when necessary [148].

Actors in the stage of agenda setting

Actors in the agenda setting (PI) should work as a multidisciplinary team. The agenda setting process should involve a wide range of stakeholders through a consultative procedure [137]. First, drugs may be selected by various groups of experts, including representatives of the national public health committee or council and the national drug formulary committee, including representatives of the ministry of public health, together with health specialists [140]. Second, the government may establish a committee for identifying alternative measures to promote access to the drugs in question. This process may require an expert body, as a broad-based committee including policy analysts and technical staff with appropriate knowledge and skills [140]. For example, the Ministry of Trade or equivalent should be involved in this process because they are regularly responsible for the intellectual property issues and TRIPS. The effective use of TRIPS flexibilities may require patent specialists to consider the right under any patent necessary to promote drug access [140, 145]. In

addition, national and international experts need to be identified to provide advice and information to support activities at the agenda setting stage [140].

5.4.2 Key elements in policy formulation

Context of policy formulation

Common misconceptions of TRIPS flexibilities (C2.1): An important context for formulating the policy is the common interpretation of TRIPS flexibilities to safeguard public health interests through CL policy. The Doha Declaration affirms that “the TRIPS Agreement can and should be interpreted and implemented in a manner supportive to protecting public health and promoting access to medicines for all” [24]. However, there are a number of common misconceptions that may deter countries from using the policy. According to TRIPS Article 31, the use of CL is not restricted to situations of national emergency, but rather in the case of other circumstances of extreme urgency or “in cases of public non-commercial use” [24]. In addition, the Doha Declaration clarified that WTO members “have the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria, and other epidemics, can represent a national emergency or other circumstances of extreme urgency” [25]. To better clarify the statement, such situations exist in any number of public health crises, including, “but not restricted to”, HIV and AIDS, tuberculosis, and malaria [24]. Therefore, when a policy is formulated, the correct conception and interpretation by concerned stakeholders on the provision of TRIPS flexibilities is a contextual element that should be taken into account.

Contents of CL policy formulation

Development of a CL policy proposal (A2.1): The main objective in formulating the policy is to develop a policy proposal. For when developing a proposal, several points must be taken into account: grounds for the policy application, policy

authorities, scope, duration, remuneration and conditions of the CL implementation [24]. The details of each issue are explained below.

1. *Grounds for the policy application:* Under the TRIPS Agreement and the Doha Declaration, members have the freedom to determine grounds for issuing a CL policy. It is important to highlight the fact that the right to grant such licenses does not only depend on a state of emergency or other circumstances of urgency, but also public non-commercial use. In particular, the public non-commercial use of a patented drug through government authorities, which is called the “government use of license”, may be determined in many ways. For example, the term “public” correspondingly refers to the *purpose* of use for the public benefits. In addition, the term “non-commercial” may be acknowledged as characterising the *nature* of the operation as “not-for-profit” use. It may also be referred to the *purpose* of the use, such as the drug supply to public institutes that do not function as commercial sectors [145].

2. *Policy authorities:* According to the TRIPS Agreement, WTO members have the freedom to designate an authority to grant CLs. The appropriate authorities to issue CL policy have to be clearly identified. In most CL countries, the policy is granted by a governmental authority. The authorised agency should be provided with a reasoned justification, legal provision and clear grounds for the policy application. This must comply with restrictions under national law [148]. Authority to issue CL may also be conferred upon the courts, after lawsuits between the patent owner and the applicant for a license. It is worth noting that where CL is granted by government sectors, this could save time and resources because experts who are familiar with public health issues already involved in the process [145].

3. *Policy scope and duration:* According to the TRIPS Agreement, the policy scope and duration of CL policy should be restricted to the purpose for which the patent use was authorized. The policy should specify the scope and duration of the requested license, and CL may apply to all of the subject elements covered by a patent, or only to certain parts of a patent, or to certain uses of patented drugs. It is also suggested that authorised agencies should request the use of a patent for the full remaining term of the patent [148]. Therefore, in general, the duration to a license also should be terminated

when the situation, which leads to the grant of CL has ended and is unlikely to return [148]. In addition, national laws should be formulated to include a review mechanism, where both the patent holder and the patent user may submit requests for the discontinuation or continuation of the license use. Therefore, if during the CL period the patent owner succeeds in demonstrating that the situation leading to the grant of CL has ceased to exist, or is unlikely to reappear, the CL would have to be revoked [145].

4. Policy conditions: Common practice is that the patent owner should be notified by the patent user as soon as reasonably practicable and should also be paid with an adequate remuneration. The government authority can propose an adequate level and kind of remuneration [150]. The common rule is that remuneration should be adequate for each CL case, taking into account the economic value of the authorization [150]. However, it may be reasonable to provide a relatively low rate of remuneration to the patent owner if a government uses the policy to secure affordable medicines in response to a public health problem [140]. Finally, the time of the payment, the basis on which remuneration as calculated, payment currency, the payee bank account, and other concerned details should be specified [148].

5. Operational strategies: The period of time required to formulate the policy should be as short as possible in order to expedite the process to satisfy the public health demand. However, according to TRIPS Article 31 (i and j), the legal validity of any policy decision concerning the authorization of CL by using a patent without permission from patent owners and any decision concerning the kind and level of royalty fee provided to the patent owner, can be subject to judicial or other independent reviews by a higher authority [148]. This means that the use of CL may be significantly delayed if the patent holder appeals the validity of the license used or the kind and level of remuneration arranged under the policy. For this reason, it is suggested that CL policy may be implemented even while appeal processes are pending [148].

Key elements to support this activity: there are additional supportive instruments for developing CL policy proposal. The supportive instruments are **national laws incorporating TRIPS flexibilities**. It is suggested that countries should include the public health safeguards of TRIPS in national IP laws and regulations [137]. In

addition, if the authorised agencies want to use the policy, but lack domestic production capacity, procurement authorities may request a foreign country to grant a CL for export [140]. Countries with the potential to export generic drugs have to include the CL for export into its laws. Therefore, legislations have to be in place both in exporting and importing countries. The World Bank provides notification models, which could be used by exporters and importers [151].

Identification of generic drug sources (A2.2): At the policy formulation stage, it is essential to identify the availability and quality of generic drug products. The authorised agency should identify sources of generic drugs and investigate whether drug manufacturers have sufficient capability to supply drugs under the expected demand. The authorised agency may identify sources of generic drugs from local producers or foreign manufacturers [24]. The WHO list of prequalified medicinal products (especially essential medicines for priority diseases) is a useful supporting tool for this, and details are explained in the next section. In addition to the WHO prequalification list, verification may be conducted through manufacturer certification provided by national drug regulatory agencies. However, capacities of the national drug regulatory agencies and requirements of national good manufacturing practices vary across countries [140]. It is therefore suggested that countries should gather information from several reliable procurement bodies, institutions and governments, which already have experience of given suppliers [140].

Key elements to support this activity: there are additional supportive instruments to identify sources of a generic drug. The supportive instrument are **lists of prequalified generic medicines** established by reliable organizations. Global initiatives for prequalification of essential medicines are beneficial for the authorised agencies of countries lacking the capacity to assess the quality of generic products. For example, the WHO List of Prequalified Medicinal Products contains a comprehensive list of prequalified generic products and manufacturers that is reviewed and updated at regular intervals [139]. The list is the result of close cooperation between national regulatory bodies and the WHO, listing medicines for HIV/AIDS, malaria, tuberculosis, influenza, neglected tropical diseases, diarrhoea, and reproductive health [152]. This project's key

strategies are: to evaluate the quality, efficacy and safety of drugs, based on manufacturer evidence and inspection from the corresponding industrial and clinical sites; to prequalify sources of active pharmaceutical ingredients (API) by comprehensively evaluating the quality of the API based on evidence developed by the manufacturers, and inspection from the corresponding industrial sites; and to prequalify laboratories of quality control for pharmaceutical products [152]. The list of prequalified generic drug manufacturers is a key instrument to enable authorised agencies to investigate the availability of generic drug manufacturers and to prepare the products for procurement in the implementation stage.

Development of streamlined procedures (A2.3): It is suggested that countries adopt streamlined administrative procedures for issuing CL policy and consider approaches to prevent any injunction, which may delay policy operation [24]. Several streamlined procedures should be used in the process of CL generic drug production and registration in preparation to supply the drug upon policy implementation. The TRIPS agreement allows countries to use provisions called “regulatory exception” or “bolar provision” that permit generic drug manufacturers to obtain marketing approval without the patent holder’s permission [146]. Therefore, countries should adopt the bolar-provision as the exclusion from patent rights, which allows CL generic producers to prepare generic drug registrations prior to the CL policy implementation [24]. In addition, countries should establish a fast-track procedure to register CL drugs, in particular for any country where drug registration is essential before launch into the local market [140]. The fast-track registration process should be reserved for certain categories of medicines such as well-established generics (as manufacturing facilities and quality of active pharmaceutical ingredients are assured or where a product is approved by qualified laboratories) [140]. Therefore, countries with local medicine registration systems should take advantage of this measure to accelerate the CL implementation.

Key elements to support this activity: in addition to the prequalified generic drugs, there are other additional instruments, which are essential in the streamlined procedures. Supportive instruments for developing streamlined CL implementation

procedures are **lists of prequalified quality control laboratories**. Agencies authorised to control generic drug quality should also be prequalified through international standard approaches, and the generic drugs should be fully approved through a comparison of quality, efficacy and safety against its reference biotherapeutic product [153]. The WHO has established a list of prequalified quality control laboratories; on 11 March 2016 the (updated) list contained 41 quality control laboratories, which had volunteered to participate in the WHO prequalification procedure and had met WHO standards [154]. The WHO also provides guidance on good practice for pharmaceutical quality control laboratories (GPCL) and on the related parts of good manufacturing practices (GMP). The guidance was developed through an international standardised quality assessment procedure [155]. Therefore, any generic drug manufacturers, which aim to supply their product under CL policy should submit their products for quality assurance in certificated laboratories, thus avoiding the need to undergo quality assurance procedures in each country to which they aim to export. This practice could improve the speed and efficiency of procedures to assure drug quality.

Actors in the stage of policy formulation

Actors in policy formulation (P2) Policy formulation requires collaboration between health, industry and trade sectors. If the government aims to produce the drugs locally, sharing information between health and industry sectors should better orient existing local industries to serve public health needs [140]. Experts from each ministry should provide technical assistance in expounding legal requirements for procedures under their authorities to address any problems that may occur during policy formulation. Experts at national, regional, or international levels should provide information and advice to support technical assistance, policy analysis and capacity building at the national level [140]. Comprehensive cooperation among concerned ministries and government partners seems to be essential to policy formulation.

The framework for policy implementation and monitoring

Figure 5.4 shows key elements for the implementation of CL policy. The previous section mentioned the stages of agenda setting and policy formulation as the first and second stages of the policy process. This section explains the third and fourth stages in the policy process. Ten elements were identified from the literature review.

The third stage in the policy process is policy implementation. Six common elements were identified:

- **One contextual element:** the capacities of agencies implementing the CL policy (C3.1).
- **Four activities:** production or procurement of generic CL drugs (A3.1), quality assurance of CL drugs (A3.2), distribution of CL drugs to health care facilities (A3.3), and utilisation of CL drug at health care facilities (A3.4);
- **One set of actors:** Authorised implementing agencies, generic firms, and international concerned agencies (P3).

The fourth stage in the policy process is policy monitoring. Four common elements were identified:

- **One contextual element:** institutional capacity to monitor performance and evaluate implications (C4.1).
- **Two activities:** performance monitoring and evaluation of policy implications (A4.1) and the development of policy feedback to improve performance (A4.2);
- **One set of actors:** Authorised monitoring agencies (P4)

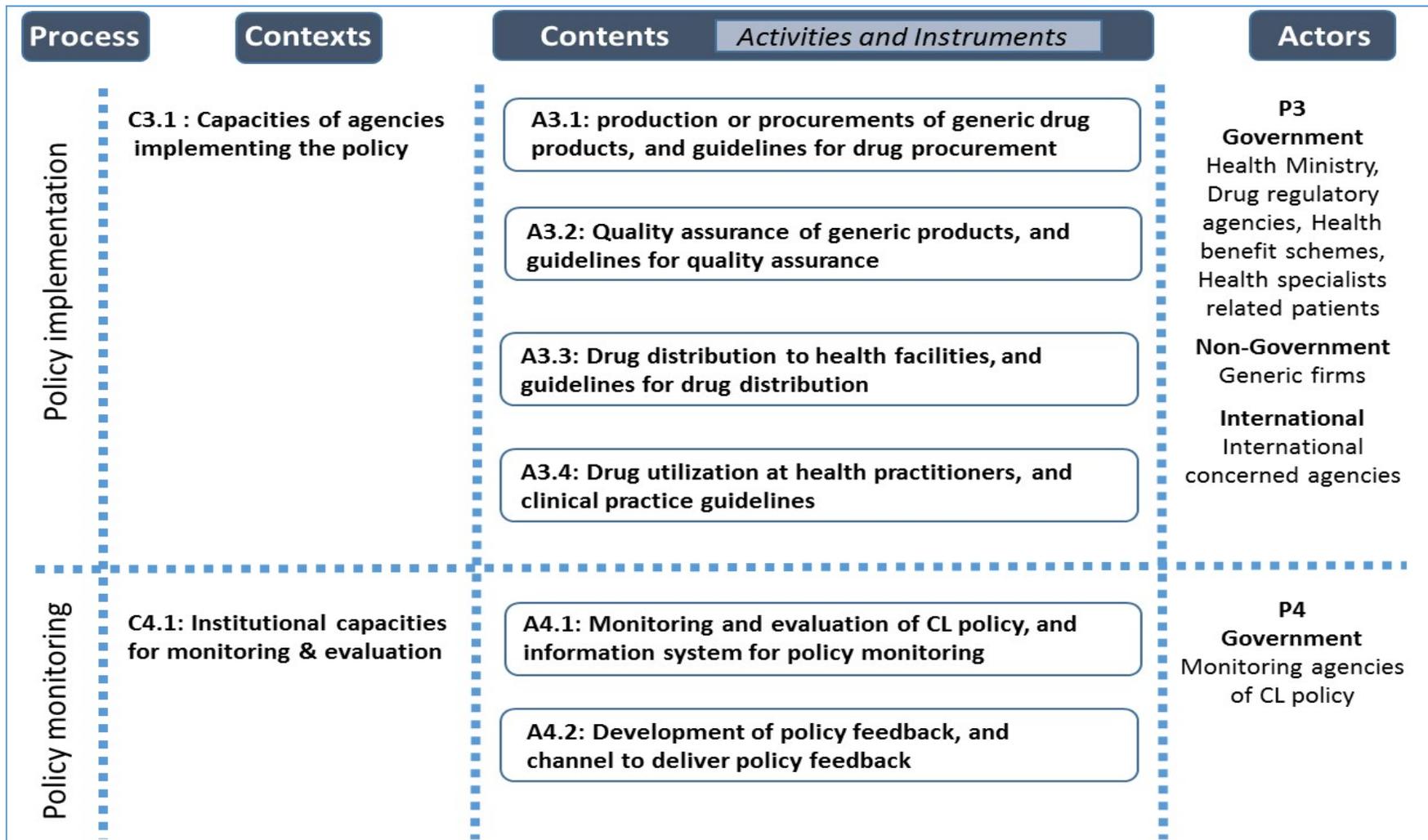


Figure 5. 4 The preliminary framework for policy implementation and monitoring

5.4.3 Key elements in policy implementation

Context of policy implementation

Capacities of agencies implementing CL policy (C3.1): Depending on domestic law, any applicant aiming to utilise CL policy may need to provide evidence of sufficient capacity to implement it [148]. Therefore, the capacity of local implementing agencies in terms of financial and resource requirements, personnel qualifications and infrastructure, are the key contextual element influencing the sustainability of CL policy implementation. The personnel should have sufficient expertise to carry out their responsibilities in the implementation process [140]. In addition, an efficient and successful infrastructure depends on adequate funding, so authorised agencies should not make a commitment, which exceeds their internal capacities and resources, because resources will have to be allocated to fulfil the commitments [140]. Local capacity should be strengthened throughout the policy implementation stage: medicine production, import, export, distribution, and utilisation, and ensuring they follow internationally accepted standards [137]. Therefore, where authorised agencies demonstrate adequate capacity throughout the implementation stage, this undoubtedly acts as the main structural context, which enables successful policy implementation [139, 140].

Contents of policy implementation

Procurement of generic drug products (A3.1): As the aim of procurement is to obtain the required generic drugs at the right time, in the correct quantities, and at the most favourable prices, meeting the public health need and complying with agreements between drug suppliers and the procurement agency [140]. Authorised procurement agencies should carefully select and procure qualified generic drugs from potential drug manufacturers. There are three key procurement activities, and each activity requires **guidelines for drug procurement** as a supportive instrument. In this section, the drug production, importation and tendering activities are included, and the recommendations of each activity are provided below.

First, recommendations where countries have sufficient manufacturer capabilities: the drugs under the CL policy may be obtained through direct production or technology transfer. Technology transfer refers to the process by which a developer of a generic drug transfers knowledge/know-how and makes its technology available to the recipients exploiting the technology. If technology transfer is pursued, recipients have to acquire knowledge, and replicate and adapt the new manufacturing technology to local conditions [156]. Therefore, the key supportive instruments seem to be guidelines on how local generic industries can best choose and replicate new technologies for equipping the transferred technology with its indigenous technologies [157]. The local industries may adopt the guidelines of technology transfer in pharmaceutical manufacturing developed by the WHO [156].

Second, *recommendations for* any country that lacks production capacity: the countries can pursue direct importation of generic drugs made under CL policy from foreign suppliers. It is possible to rely on procurement by international non-profit organisations who have experience with the procurement of generic drug products [139]. It is clear that directly importing CL drugs can save more time than using technology transfers. However, the selection of foreign drug suppliers should be carefully conducted because weak suppliers can impede supply chain performance and create unnecessary costs. The supportive instrument in this activity is guidelines for selecting generic drug products and suppliers based on evaluations of individual medicine dossiers and compliance with good manufacturing practices (GMP), respectively [139]. The details of common practices have been published by WHO [158].

Third, *recommendations for* drug tendering: competitive open tenders are recommended for pharmaceutical procurement [159] as these provide all qualified generic drug suppliers with an equal opportunity to participate. In most cases, a grant is based on the most attractive proposal from candidate suppliers who are able to meet the terms of the tender [139]. Procurement agencies should comprehensively scrutinise and continually monitor the performance of qualified suppliers, and monitor price trends of qualified medicines through comprehensive tendering information [137]. Therefore, the supportive instruments required in this activity are tendering guidelines and an information system, which is

comprehensive, accurate and timely. The information system under CL policy should be able to: produce information for drug quantification and tendering processes; compare suppliers' offers for procurement decisions; formulate notifications of award and purchasing orders; track the purchasing order status and compliance with agreed procurement contract terms; arrange effective communication with contract drug suppliers; and monitor performance of drug suppliers for future tenders. All general issues to be considered in the tendering process are mentioned in the WHO guidelines [159].

Quality assurance of generic products (A3.2): The aims are to make health personnel trust the quality and therapeutic effectiveness of CL generic drugs compared to patented versions [139]. Parts of the assurance procedures (product registration and pre-marketing regulation) may be conducted from the policy formulation stage. Post-marketing, after the drugs are launched into the market, generic versions must be regularly monitored to ensure consistent quality. The purpose of post-marketing control is to ensure that the quality of generic drugs distributed to consumers consistently complies with drug standards [139]. GMP compliance inspections of generic drug factories must be conducted together with an analysis of product samples by an accredited laboratory to ensure compliance with legal requirements [139]. The inspections aim to enforce GMP compliance and monitor drug quality throughout the supply chain, from manufacture to delivery to the patients. This could improve the confidence of practitioners and patients in the quality, effectiveness and safety of CL drugs, helping them believe that the drugs are equivalent to patented drugs and meet international standards.

Key elements to support this activity: there are additional instruments, which are essential in the quality control activities of generic drugs. The supportive instruments in this activity are **guidelines for quality assurance of generic drugs**. Quality control refers to the procedures attempting to ensure the identity and purity of certain pharmaceutical substances in compliance with acceptable standards. The WHO formulated a series of guidelines on quality assurance procedures from simple chemicals to more complex pharmaceutical products [160]. In addition, the WHO developed regulatory standards on related issues, including bioequivalence, stability, packaging and storage [161]. Moreover, it is important to support the establishment of functional mechanisms to monitor the quality of pharmaceutical products

throughout distribution channels, from the point of production to delivery to the users. The WHO also developed guidelines for inspections of drug to ensure the safety of medicines [162].

Drug distribution to health facilities (A3.3): Mechanisms are required to secure the constant availability of qualified drugs for all health care facilities in need. It is suggested that drug products should be obtained from the authorised supply chain and reliably stored, transported and handled under conditions which comply with predetermined standards, as required by product specifications, until the drugs reach local health care facilities [163]. In addition, authorised drug distribution agencies should identify competent mechanisms to improve the accuracy and efficiency of the drug inventory system through an availability of accurate, updated, and accessible information on the drugs for concerned parties. The required characteristics of drug distribution systems are as follows: (1) constant supplies of drugs should be secured, (2) drugs should be distributed in good condition until they reach the patient, (3) losses due to damage, spoilage or expiration should be diminished, (4) theft and fraud should be strongly prevented, (5) accurate inventory information should be constantly maintained, (6) rational storage sites should be organized for security, timely supply, and quality maintenance, (7) transportation resources should be used efficiently, and (8) accurate and comprehensive information should be continually collected for predicting drug needs [140].

Key elements to support this activity: there are additional instruments, which are essential in the activity of drug distribution. The supportive instruments for distributing CL drugs to health care facilities are **guidelines for drug distribution**. The WHO has developed a number of international standard guidelines concerning drug supply chain management [164], and authorised agencies may apply the guidelines to inspect drug distribution channels. In addition, it is suggested that countries should strengthen collaboration and information-sharing between those responsible for drug supply management, and those responsible for public health programs, to increase the efficiency of the supply chain system [137]. The ultimate aim is to ensure that adequate supplies of qualified drugs are constantly provided to health care practitioners and patients at every level of health care facility.

Drug utilisation by health practitioners (A3.4): The utilisation of drugs at health facility units requires the provision of medicine information, encouragement of rational drug use, and supervision of drug utilisation [140]. Activities to promote drug utilisation in compliance with national drug policy are as follows: (1) strengthening mechanisms for drug information-sharing and developing up-to-date clinical practice guidelines; (2) advocating the incorporation of training modules and continuing education programmes on rational use of medicines for health care workers. This is because supportive and educational supervision of rational use in compliance with the clinical practice guidelines is more effective and better accepted by prescribers than regular inspection and penalty; (3) supporting the monitoring of practitioner prescribing practices according to the guidelines [165]. Effective monitoring methods of drug utilisation are prescription audit and feedback. Audits should check whether prescribers' prescriptions comply with accepted guidelines or policy protocol [165]. This provision is essential to ensure the good practice of health care professionals at health care facilities.

Key elements to support this activity: there are additional instruments, which are essential in the activity of drug utilisation. The supportive instruments for utilising drugs at health care facilities are **clinical practice guidelines**. The utilisation of CL drugs at hospital units requires activities to promote rational drug use. Authorised central agencies may establish expert committees to develop guidelines related to rational drug use. Evidence-based clinical practice guidelines and prescribing policies play an important role in helping prescribers to choose proper treatments for particular clinical conditions. To promote rational drug use, the development of clinical practice guidelines should take into account the following points: (1) they should be developed with the participation of prescribers as the end-users; (2) the guidelines should be easy to read and supported with an official introduction, continuous training and extensive dissemination; (3) the guidelines should be reinforced through prescription audit and user feedback; (4) the guidelines should be regularly updated in order to assure credibility and acceptance by health care practitioners [165]. Practitioners need to provide health care services in compliance with clinical practice guidelines, but some may have difficulty changing their traditional practices to meet the guidelines, or may be unwilling to comply with

the new policy. Therefore, adherence to guidelines in local hospital units may be measured in the form of utilisation review under an auditing system [165].

Actors at the stage of policy implementation

Actors in policy implementation (P3). Authorised implementing agencies consist of drug procurement, quality assurance, distribution and utilisation. First, drug procurement agencies may request useful advice and guidance from country, regional or international procurement agencies. Some international organisations, such as UNICEF and the World Health Organization's Essential Drugs and Medicines Policy (WHO/EDM), as well as NGOs such as MSF and the International Dispensary Association (IDA), have long experience in drug procurement and have established procedures for this matter. They can provide product lists, specify sources of drugs, and assist in comparing drug prices [140].

Second, in terms of quality assurance, domestic laboratories approved by the national drug regulatory authority should participate in the WHO prequalification system for quality control laboratories and plan for the enhancement of their capacity for both local and foreign demands. In addition, laboratories of international non-profit procurement agencies and private laboratories may be acceptable if they meet international requirements; for example, laboratories which are accredited by private agencies such as International Organization for Standardization (ISO) and Organisation for Economic Co-operation and Development (OECD) norms and standards [140].

Third, the government may authorise an organisation, which has expertise in national drug management systems to be responsible for drug distribution and utilisation management, and local health care professionals may participate in the implementing process at their facilities [140]. It is suggested that countries should develop a system to strengthen personal expertise and local infrastructures to ensure appropriate management of the drug supply system at all levels of health facilities. The link between each stage is essential, for example, supporting collaboration between the national drug procurement agency and the national drug regulatory agency to prevent the risk of purchasing poor quality drugs from unqualified suppliers [137].

5.4.4 Key elements in policy monitoring

Context of policy monitoring

Institutional capacity to monitor performance and evaluate implications

(C4.1): When a policy is implemented, not only should the performance of implementing organisations be monitored, but implications of policy implementation should be evaluated, in order to provide information on whether the policy has achieved the expected outputs and outcomes. Therefore, the institutional capacity of authorised agencies to monitor policy performance and evaluate policy implications seems to be a key structural contextual element at this stage. By strengthening the institutional capacity of both central and local agencies, the monitoring agency should be equipped with capable workers and sufficient resources to monitor performance and evaluate policy implications [166]. This aims to provide evidence and information to help policy makers decide whether to continue, improve, or discontinue the policy; as well as to develop strategies for improving the efficiency and effectiveness of the policy [137].

Content of policy monitoring

Monitoring and evaluation of CL policy (A4.1): To monitor policy performance, local authorised agencies should conduct routine reporting of performance data through a system of information management. This activity may require close supervision from a central or national agency through continual monitoring of implementation and progression. In addition, if any unanticipated situation occurs, more detailed reporting and monitoring (for example sentinel sites or special studies) are essential in order to develop strategies to resolve problems [140]. The key activities in this stage are as follows: (1) the central agency should implement indicator-based monitoring of policy performance with the aim of guiding local agencies to collect adequate information to evaluate policy outputs and outcomes. (2) Workers in local agencies should be advised on the adoption of

indicator-based tools to monitor policy implementation. (3) Throughout the monitoring stage, the central agency should monitor policy implementation at intervals adequately frequent for the management purpose with local agency [137]. Information obtained from the activities mentioned above could be beneficial to develop strategies to improve performance and maximise benefits of the policy.

Key elements to support this activity: there are additional instruments, which are required to support the monitoring and evaluation activities. The supportive instruments for this activity are **information systems for policy monitoring**. The policy monitoring stage requires an effective data collection system for gathering inputs and outputs. Indicators for data collection should be chosen wisely to provide adequate, accurate and reliable information to the central or national agency who need it for management and planning [140]. Monitoring indicators should be selected based on local conditions, such as implementation means and resources available, with the aim of maximising the effectiveness and efficiency of data collection. The required features of data monitoring systems are as follows: (1) improved links between systems of data generation, monitoring and evaluation, in order to generate the most beneficial data and avoid underutilization; (2) harmonisation of multiple data collection and reporting systems to reduce unnecessary duplication. [140].

Development of policy feedback (A4.2): Findings from the policy monitoring stage can be used to develop feedback on the problems, obstacles, and defects arising during policy implementation and to develop strategies to resolve problems and improve performance [166]. Therefore, countries should use policy monitoring information to refine policy implementation by communicating with national policy-makers, system managers, health workers and drug user groups. The feedback could provide suggestions to improve performance in a specific activity in any policy stage (agenda setting, policy formulation, and policy implementation), and could connect a relationship between each policy stage in order to present a full and honest pictures of end results. In addition, countries should also provide lessons learnt from their experiences and share the information to contributions to literature on national, regional and global trends [137].

Key elements to support this activity: there are additional instruments, which are required to support the policy development feedback. The supportive instruments in this activity are **channels to deliver policy feedback**. There were several issues to consider when initiating channels to deliver policy feedback to decision makers and stakeholders. A broad range of stakeholders is involved in the policy process, including policy planning and development, health system management, health service management, and advocacy. Each level has diverse technical disciplines with specific terminological expressions and communication approaches. Therefore, dissemination should be wisely developed for each stakeholder, and the most effective campaign and communication channel to deliver policy messages should be judiciously chosen. The timing of information dissemination should also be scheduled to fit in with each policy process and the needs of the intended recipients [24, 137]. This instrument plays an important role in the effective achievement of any policy.

Actors at the stage of policy monitoring

Actors in policy implementation (P4). Implementing agencies should play an important role in monitoring their performance all the way through the policy process. Local authorised agencies have to closely monitor policy performance with technical and policy staff to ensure the process is efficient and effective [140]. In addition, as the activities in the monitoring and evaluation process involve all local authorised agencies across the country, the central or national authority should be a moderator and/or supervisor to facilitate and supervise all concerned sectors [140]. Moreover, policy feedback should not only be delivered to the authorised agencies but also to the public. Therefore, other domestic and international stakeholders such as healthcare workers, academics, civil society and the private sector should receive accurate and timely information to help them keep track of the policy situation. They may be asked to participate in the policy if necessary [137].

5.5 Discussion and conclusions

In this chapter, a preliminary framework was developed by identifying policy elements from generic recommendations from inter-governmental organisations.

The identified elements were analysed and classified into four sections: policy contents, context, actors and process, according to the policy triangle model of Walt (2005) [128]. Regarding the research findings in this Chapter, 21 policy elements were identified as essential, to be included in the framework. The framework assumed that the policy process can be classified into four stages, including agenda setting, policy formulation, policy implementation and policy monitoring. The processes of agenda setting and policy formulation contain 6 and 5 elements respectively, while the processes of policy implementation and monitoring contain 6 and 4 elements respectively.

According to Joseph S, et.al., there are several approaches of policy analysis, namely (1) process approach to examine a part of the policy process e.g. agenda setting and policy implementation, (2) substantive approach to examine a substantive area with special expertise, e.g. environmental matters, (3) logical positivist approach to examine causes and consequences of policy using scientific methods, (4) economic approach to test economic theories, (5) phenomenological approach to analyze events through a discipline of sound intuition, which is itself born of experience not reducible to models, hypothesis, or quantification, (6) prescriptive approach to prescribe policy to decision makers or others to achieve a determined end state, (7) ideological approach to analyze from a liberal or conservative point of view which comes from within individuals rather than externally imposed by the outside environment, and (8) participatory approach to examine the role of multiple actors in policymaking [167].

Among these eight approaches, two can be useful for developing a framework which decision makers might use to help in thinking through the development and use of CL policy: (1) Process approach for examining a part of the CL policy process and (2) Participatory approach for examining the role of multiple actors in CL policy. The development of a CL policy framework requires an analysis of each policy process and the actors who participate in the process. Therefore, the policy triangle model was selected because it presents a greatly simplified approach to analyse a complex set of inter-relationships among policy elements, including policy process and actors [127]. In addition, the model has been successfully used to analyse policies in several areas of public health in Thailand, for example: a policy analysis for the Universal Coverage Schemes in Thailand [168]; a policy analysis for

the Universal Access to anti-retroviral drugs in Thailand [169]; and an analysis for the health and trade negotiation in Thailand [170]. In addition, it has been confirmed that this 'policy triangle' framework 'can be applied in any country, to any policy, and at any policy level.' [128].

However, it is noteworthy that the policy process is not always linear, as the methodology assumes. The four sections may occur in parallel during the CL policy process. For example, according to the TRIPS agreement, the legal validity of any CL decision concerning the use of patent use without permission from patent owners, and any decision concerning the kind and level of remuneration or royalty fee provided to the patent owner regarding such use, can be subject to judicial review or other independent review by courts or other authorised agencies [146]. Given this, the use of CL may be delayed if the patent owner appeals the validity of the license used or the kind and level of remuneration granted under the policy. For this reason, the government can fully implement the policy even while appeal procedures are operating [148].

The literature review found that there is limited literature contributing to the development of a CL framework. Some focused on legal issues rather than how to adopt the policy in reality. Some researches had been conducted at a very early phase of CL introduction, at which point very little practical work had been undertaken. Some focused on a specific stage of the policy and did not cover the whole policy process. Therefore, to contribute to the literature, I developed a preliminary framework for CL by identifying common policy elements affecting the process of CL policy covering the whole process of public health policy: decision-making (agenda setting and policy formulation) and policy implementation (implementation and monitoring).

However, there were limitations to this study. The aim of this chapter is to develop a preliminary framework, which is not an action plan. The implementation guideline for each content activity, for example drug procurement, transfer of production technology, quality assurance, drug distribution, and clinical practice guidelines to utilize the drugs, are available elsewhere. Therefore, I do not provide an action plan for CL policy, but I do put the available guidelines as key elements in

the content of each activity, so that readers are aware of further detail available elsewhere.

The preliminary framework was developed based on general recommendations from inter-governmental organisations, including the WHO, WTO, UNDP, UNCTAD and World Bank. However, these organizations provided policy recommendations to advise countries in general. The information omitted context-specific elements of each country such as indigenous culture, domestic policy and law, limitations of local capacity and resources. Therefore, elements of policy context in the preliminary framework were unsatisfactory in relation to guiding Thailand and required adjustment by domestic data. In addition, there is still a lack of evidence for practical implementation issues within the framework. In response to the limitations, empirical evidence and lessons from the eight-year experience of the former government in implementing CL policy were analysed in order to strengthen the contents of the framework. This is discussed in the following chapters.

Chapter 6: Lifetime treatment cost savings due to CL implementation

6.1 Introduction

The preliminary framework in chapter 5 required complementary information to strengthen the content in the framework. As the framework was divided into two sections: decision-making and implementation, chapter 6 was dedicated to analyse potential implications of CL policy in order to strengthen the “decision-making part of the framework”. There are five areas of analysis: two drugs against HIV/AIDS (efavirenz and LPV/r), one against cardiovascular disease (clopidogrel), one against lung cancer (docetaxel), and one against breast cancer (letrozole). I clarify the differences in efficacy between the CL drugs and the comparators in table 6.1.

This chapter aims to estimate lifetime treatment costs savings among patients using the CL drugs compared to its comparator. The comparative benefits in terms of the national budget savings (lifetime treatment cost savings in total population of patients) across different drug types could be used to develop drug selection criteria, in order to strengthen contents of the decision-making parts in the preliminary framework in chapter 5. Therefore, the research questions are as follows: (i) what are the differences in benefits in terms of national budget savings from the use of CL drugs compared to its comparator (the drugs which could be used without CLs)?; (ii) what are factors which create the highest benefits to the government and should be incorporated in the drug selection criteria, in order to strengthen contents of the framework?.

Table 6: Summary of comparative efficacy for CL drugs versus its comparator

	Drugs of interests	Comparative efficacy
1.	Efavirenz versus Nevirapine	Probability of patients failed treatment in Efavirenz and Nevirapine was 16.7% and 20.7%, respectively [171].
2.	LPV/r versus IDV/r	Probability of patients to obtain virological success at 12th month in LPV/r and IDV/r was 88.2% and 73.1% respectively. [172]
3.	Clopidogrel versus Ticlopidine	Rate ratio of composite of undesirable vascular events was 0.87% for clopidogrel over ticlopidine [173].
4.	Letrozole versus Tamoxifen	Patients receiving letrozole and tamoxifen had five-year overall survival at 91.8% and 90.4%, respectively [174].
5.	Docetaxel versus Best supportive care	Patients receiving docetaxel and the best supportive care had time to progression at 10.6 and 6.7 weeks, respectively; and median survival at 7.0 and 4.6 months, respectively. [175]

Note: Although the efficacy units are different across five studies of drug comparison, my study converted them into the same monetary units.

6.2 Methods

Outcomes of interest were simulated by Markov models for the five medicines. Using the government perspective, the lifetime treatment cost savings due to CL were evaluated by comparing the CL drugs with alternative drugs used prior to CL. Costs were estimated in 2015 US\$ using the exchange rate of 32.719 baht per US\$ [176]. All costs reported in earlier years were adjusted by consumer price indexes (CPIs) published by the Thai Ministry of Commerce for the price year 2015 [177]. Future costs were adjusted by using a 3% discount rate, as recommended by health technology assessment guidelines of Thailand [178].

6.2.1 Rationale for model selection

The two common types of models employed in decision analysis are decision trees and Markov models [129]. The decision tree model is the simplest form of decision models, and it is not suitable for diseases where symptoms and severity change over time. Instead of possible consequences of health outcomes over time being modelled by a large number of possible pathways in a decision tree, the more complex prognosis can be simplified by employing a Markov model. The Markov

model is commonly employed to handle the complexity of modelling options of infectious diseases for HIV/AIDS [179] and chronic diseases for stroke [180] and cancers [181]. Therefore, Markov models were used to estimate future implications of lifetime treatment costs for the five medicines.

6.2.2 Overview of options for interventions and comparators

I compared drug regimens recommended by the Thai clinical practice guidelines (CPGs) before and after CL was implemented for the five drugs. The drug regimens that the CPGs used before CL implementation were set as the counterfactual scenarios (baseline comparators). After the availability of generic drugs under the CL policy, the drug regimens recommended in the CPGs were changed, and this was set as the factual scenario. Long-term effects on lifetime cost savings were evaluated by comparing the treatment cost of CL drugs with that of its comparator used prior to CL implementation (Table 6.1).

Table 6. 1 The regimens of CL drugs and its comparators

Models	CL drugs (Factual scenarios)	Comparators (Counter-factual scenarios)
Efavirenz	Efavirenz 600 mg per day treatment of HIV/AIDS [182]	Nevirapine 200 mg every 12 hours for treatment of HIV/AIDS [118]
LPV/r	LPV/r 800/200 mg per day for treatment of HIV/AIDS [182]	IDV/r 1,600 mg per day for treatment of HIV/AIDS [118]
Clopidogrel	Clopidogrel 75 mg per day for treatment of stroke [183]	Ticlopidine 500 mg per day for treatment of stroke [184]
Letrozole	Switching therapy by tamoxifen 20 mg per day for two years followed by letrozole 2.5 mg per for three years [185]	Mono-therapy by tamoxifen 20 mg per day until completion of five-year treatment [186]
Docetaxel	Docetaxel 100 mg/m ² every 21 days (1 cycle) for 4 cycles for treatment of advance NSCLC [187]	Best supportive care as there is no other alternative treatment of docetaxel for advance NSCLC [186]

Abbreviation: LPV, lopinavir and ritonavir combination; IDV/r, indinavir and ritonavir combination; NSCLC, Non-small cell lung cancer

6.2.3 Model structure

Five Markov models for the five CL medicines were developed in Microsoft Excel 2007 (Microsoft Corp., Redmond, WA, USA). The Markov models for each medicine are shown in Figures 6.1 – 6.5. The cycle length of moving from one health state to another was set at 1 year. The time horizon was patients' lifetime. The treatments with ARVs and cancer drugs were modelled by three health states: treatment responsiveness, disease progression and death. The treatment responsiveness refers to the health state of patients who respond to the treatment, while the disease progression refers to the health state of patients who failed to respond the treatment. Clopidogrel is used for stroke prevention. This model contains three health states: secondary prevention of stroke, disease progression, and death. Patients remain in the first health state until the next cycle. Moving to the other health states depends on the disease progression during treatment. The arrows in the figures represent the transitional possibilities of patients moving from one health state to another at the end of each cycle length. Some patients might die at the end of each cycle.

Efavirenz model: Since CL was implemented, efavirenz has been recommended by the Thai CPGs as the first-line therapy for patients living with HIV. The starting age of the patient group used in this study was assumed as 30 years, as an average age of HIV/AIDS patients in Thailand [118]. If the patients respond to the first-line treatment by the efavirenz or nevirapine (the counterfactual), they stay in the treatment responsiveness state. However, some patients may have treatment failure and move to the disease progression state, or may move to the death state (Figure 6.1).

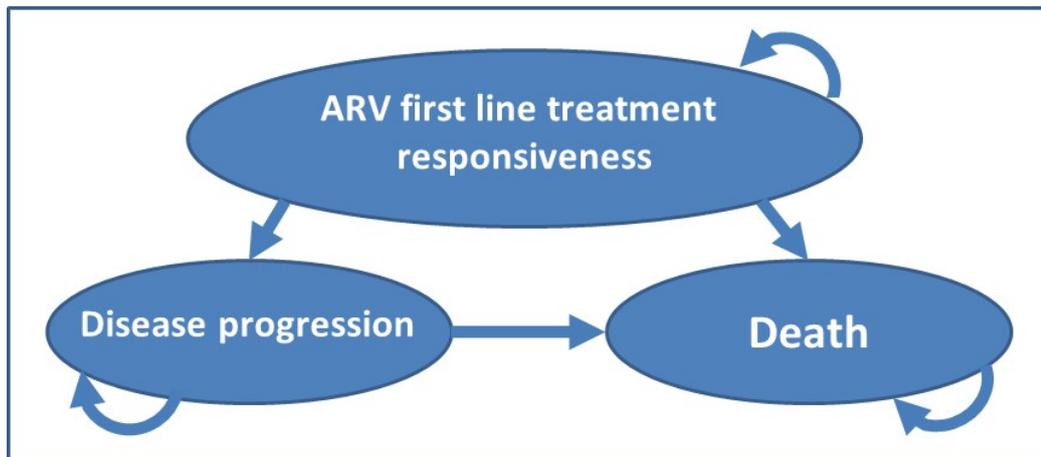


Figure 6. 1 The Markov model structure used for the first line ARV treatment of efavirenz

LPV/r model: Since CL, LPV/r has been recommended by the Thai CPGs as second-line therapy for patients living with HIV. Similarly to the efavirenz model, the starting age of the cohort was assumed as 30 years [186]. Patients can stay in the treatment state if their symptoms respond to the second-line treatment of LPV/r or IDV/r (the counter-factual). However, some patients may fail to respond and move to the disease progression state of HIV/AIDS, or may move to the state of death (please see 6.2).

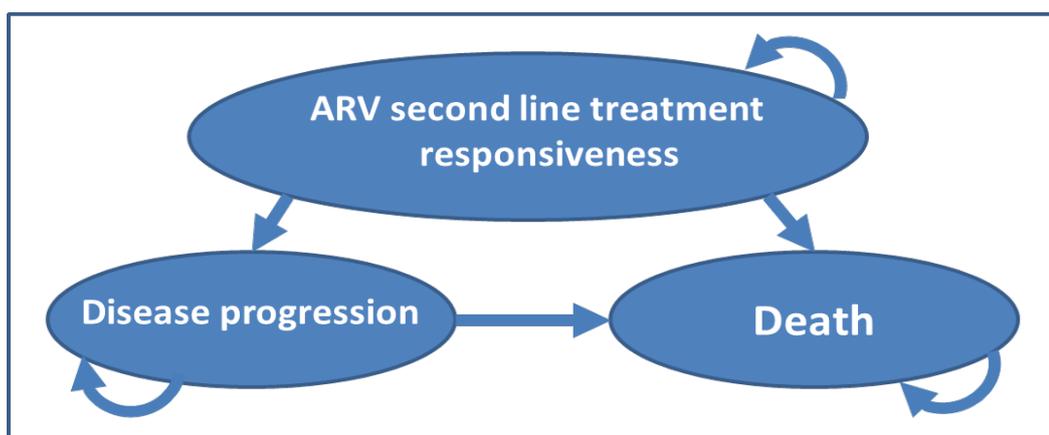


Figure 6. 2 The Markov model structure used for the second line ARV treatment of LPV/r

Clopidogrel model: Clopidogrel is recommended by the Thai CPGs to use for secondary prevention for patients with stroke. The starting age of the cohort was assumed as 60 years, as an average age of patients requiring secondary stroke prevention in Thailand [186]. The patients can stay in the treatment state if their symptoms respond to the treatment. However, some patients may fail to respond and have a secondary stroke. The patients then move to the progression health state of secondary stroke or may move to the state of death (please see 6.3).

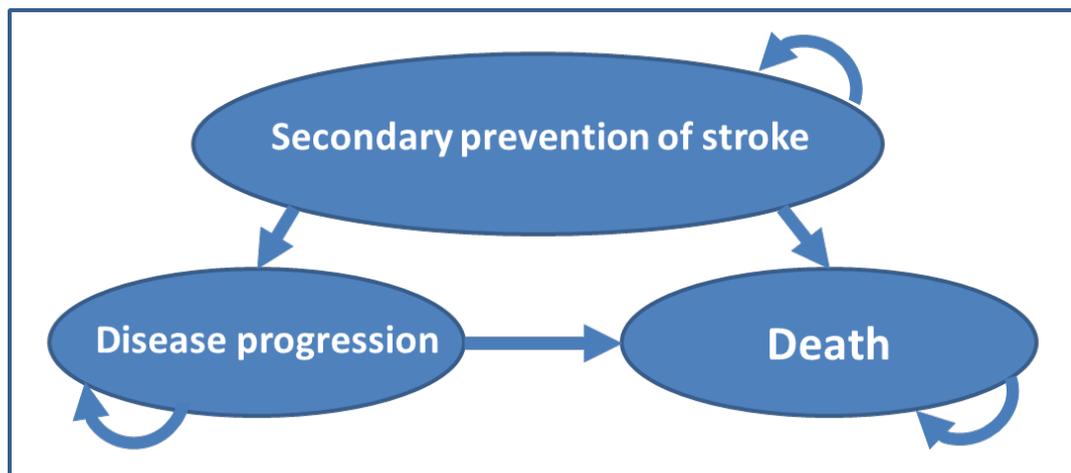


Figure 6. 3 The Markov model structure used for the secondary prevention of stroke

Letrozole model: Letrozole is recommended by the Thai CPGs to use for patients with breast cancer. The starting age of is the cohort was assumed as 60 years, as an average age of postmenopausal breast cancer patients [186]. The patients can stay in the treatment state if their symptoms respond to the treatment. However, some patients may have treatment failure and move to the disease progression state of breast cancer, or may move to the state of death (please see 6.4).

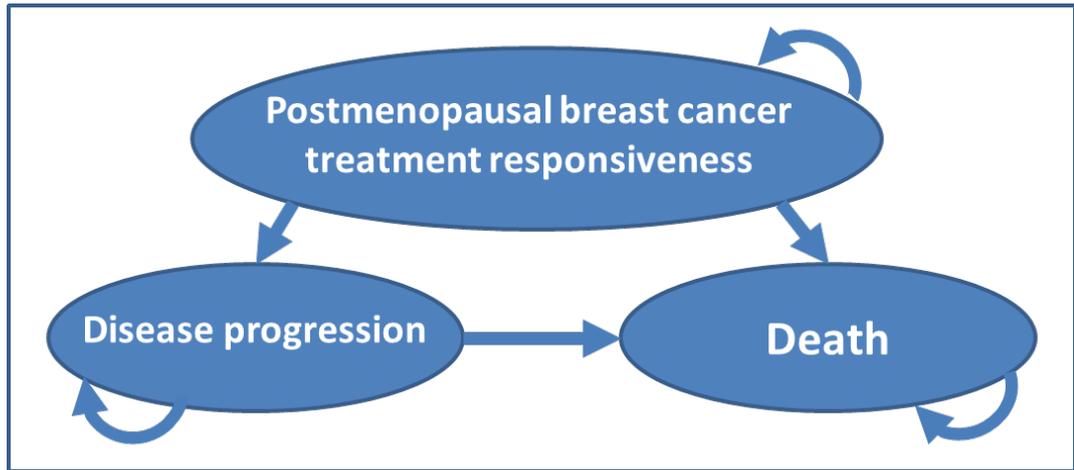


Figure 6. 4 The Markov model structure used for the postmenopausal breast cancer

Docetaxel model: Docetaxel is recommended by the Thai CPGs to use in patients suffering from advanced stage of non-small cell lung cancer (NSCLC). The starting age of is the cohort was assumed as 60 years, as an average age of advanced stage NSCLC [186]. The patients can stay in the treatment state if their symptoms respond to the treatment. However, some patients may have treatment failure and move to the progression state of lung cancer, or may move to the state of death (please see 6.5).

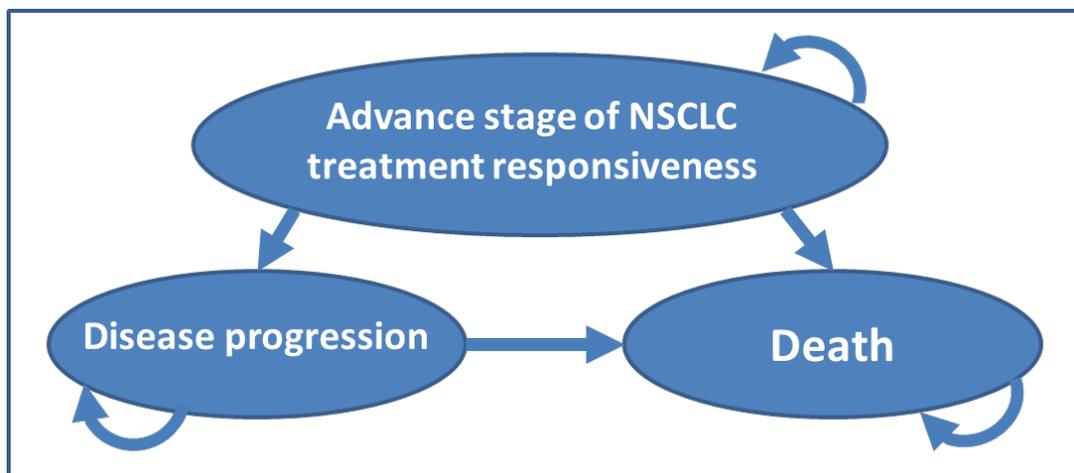


Figure 6. 5 The Markov model structure used for the non-small cell lung cancer (NSCLC)

6.2.4 Model Parameters

6.2.4.1 Transitional probability of changing health states: An extensive literature review was conducted and several relevant studies that compared treatments of interests were identified. The PubMed database was searched using the specific keywords and identified literature was analysed according to the inclusion criteria as follows. (1) Studies written in English and Thai, (2) Studies conducted clinical treatment protocol consistent with the drug indication and regimens recommended by the Thai clinical practice guidelines, and (3) Studies conducted to measure outcomes of interest consistent with those analysed in this study.

Four types of parameters were identified: (1) Transitional probabilities of patients moving from the treatment responsiveness to the disease progression and directly to death were used as baseline parameters. The parameters obtained from cohort studies and observational studies. Studies that provided the most comprehensive set of parameters for defined health states were selected. (2) Relative risks to prevent disease progression and death by the CL drugs compared to its comparator were used to multiply with the baseline transitional probabilities, in order to estimate the benefits of treatment by the CL drugs over its comparators. The relative risk parameters were selected from the most up to date studies, and study types included systematic reviews and meta-analysis if available. (3) The transitional probabilities of patients moving from disease progression to death were obtained from Thai studies because they were usually affected by the context-specific of the Thai health care system. (4) The probability of disease complications and adverse events from the treatment were obtained from cohort studies and observational studies that provided the parameters of treatments in question of my study. The findings of the parameter review are summarised as follows.

Efavirenz: For the efavirenz as the first line treatment of HIV/AIDS, the search term was Human Immunodeficiency Virus [MeSH Terms] AND efavirenz AND nevirapine. The identified parameters show in Table 6.2. The baseline transitional probabilities of nevirapine to prevent disease progression and death of nevirapine at 0.15 and 0.02, respectively were obtained from a randomised controlled trial study [188]. For the relative risk of progression and dying of

efavirenz compared to nevirapine at 0.75 and 0.81, respectively, were obtained from a meta-analysis study [171]. In addition, there are common adverse events of the drugs during the treatment period. These probabilities were obtained from a Thai thesis [189]. The yearly probabilities of adverse events occurred for nevirapine contain skin reaction, SJS, hepatitis, hepatotoxicity and high triglyceride at average 0.13, 0.012, 0.025, 0.025 and 0.029 respectively [189]. The yearly probabilities of adverse events occurred for efavirenz contain skin reaction and high triglyceride at 0.009 and 0.162 respectively. The transitional probability of dying among patients after disease progression at 0.029 was obtained from Thai cohort study [190].

Table 6. 2 Treatment effect parameters of efavirenz and its comparator

Parameters	Means	References
Transitional probability of progression (baseline)	0.15	[188]
Transitional probability of dying (baseline)	0.02	[188]
Relative risk of progress of efavirenz compared to nevirapine	0.750	[171]
Relative risk of dying of efavirenz compared to nevirapine	0.810	[171]
Probabilities of skin reaction events of nevirapine	0.13	[189]
Probabilities of steven johnson syndrome events of nevirapine	0.012	[189]
Probabilities of hepatitis events of nevirapine	0.025	[189]
Probabilities of hepatotoxicity events of nevirapine	0.025	[189]
Probabilities of high triglyceride events of nevirapine	0.029	[189]
Probabilities of skin reaction events of efavirenz	0.009	[189]
Probabilities of high triglyceride events of efavirenz	0.162	[189]
Transitional probability of dying with HIV/AIDS progression	0.029	[190]

LPV/r model: For LPV/r as the second line treatment of HIV/AIDS, the search terms were Human Immunodeficiency Virus [MeSH Terms] AND lopinavir AND ritonavir AND indinavir. The identified parameters are shown in Table 6.3. As no meta-analysis study providing relative risks of LPV/r compared to IDV/r was found, I used parameters of transitional probabilities from single studies. The transitional probabilities to prevent disease progression and dying of LPV/r at 0.06 and 0.01, respectively, were obtained from an observational study [172]. The transitional probabilities to prevent disease progression and dying of IDV/r at 0.29 and 0.02, respectively, were also obtained from observational studies [172, 191]. In addition, there were adverse events during the treatment period equivalent for both drugs. The yearly probabilities of adverse events occurred for rash, clinical hepatitis and neutropenia were at 0.135, 0.173 and 0.019 respectively [190]. The transitional probability of dying among patients in the disease progression at 0.036 was obtained from a Thai cohort study [190].

Table 6. 3 Treatment effect parameters of LPV/r and its comparator

Parameters	Means	References
Transitional probability of progression of patients using IDV/r	0.29	[172]
Transitional probability of dying of patients using IDV/r	0.02	[191]
Transitional probability of progression of patients using LPV/r	0.06	[172]
Transitional probability of dying of patients using LPV/r	0.01	[172]
Probabilities of hepatitis events of patients using IDV/r	0.173	[190]
Probabilities of skin rash events of patients using IDV/r	0.135	[190]
Probabilities of skin rash events of patients using LPV/r	0.018	[190]
Probabilities of neutropenia events of patients using IDV/r	0.019	[190]
Probabilities of neutropenia events of patients using LPV/r	0.018	[190]
Transitional probability of dying with HIV/AIDS progression	0.036	[190]

Clopidogrel model: For the clopidogrel as the secondary prevention of stroke, the search terms were Stroke [MeSH Terms] AND clopidogrel AND ticlopidine. The identified parameters are shown in Table 6.4. The relative risk of progression and dying of clopidogrel compared to ticlopidine at 0.87 and 0.97, respectively, were obtained from a meta-analysis [173]. For the baseline transitional probabilities to prevent disease progression and dying of ticlopidine at 0.352 and 0.005, respectively, were obtained from a multicenter randomised control trial study [192]. In addition, the main adverse event of the drugs during the treatment period is neutropenia. The yearly probabilities of adverse events occurred for ticlopidine and clopidogrel at 0.023 and 0.010 respectively were obtained from a systematic review [193]. Transitional probability of dying among patients after disease progression at 0.073 was obtained from a national data of stroke outcomes in Thailand [194].

Table 6. 4 Treatment effect parameters of clopidogrel and its comparator

Parameters	Means	References
Transitional probability of progression (baseline)	0.352	[192]
Transitional probability of dying (baseline)	0.005	[192]
Relative risk of progress of clopidogrel compared to ticlopidine	0.870	[173]
Relative risk of dying of clopidogrel compared to ticlopidine	0.970	[173]
Probabilities of neutropenia events of ticlopidine	0.023	[193]
Probabilities of neutropenia events of clopidogrel	0.010	[193]
Transitional probability of dying with stroke recurrence	0.073	[194]

Letrozole model: For the letrozole as the treatment of early stage breast cancer, the search term is Breast Neoplasms [MeSH Terms] AND letrozole And Tamoxifen. The identified parameters are shown in Table 6.5. The relative risk of disease progression and dying of switching-therapy compared to mono-therapy at 0.8 and 0.82, respectively, were obtained from a meta-analysis [174]. The baseline transitional probabilities to prevent disease progression and dying of tamoxifen in monotherapy at 0.006 and 0.005, respectively, were obtained from a randomise double-blind trial [195]. In addition, the main ADR for breast cancer treatment is virginal breeding. The yearly probabilities of adverse events occurred during the treatment of tamoxifen and letrozole were at 0.091 and 0.042, respectively [195]. Transitional probability of dying among patients after disease progression at 0.394 was obtained from a cancer surveillance in KhonKhan provinces in Thailand [196].

Table 6. 5 Treatment effect parameters of letrozole and its comparator

Parameters	Mean	Reference
Transitional probability of progression (baseline)	0.006	[195]
Transitional probability of death (baseline)	0.005	[195]
Relative risk of progression of switching compared to monotherapy	0.800	[174]
Relative risk of death of switching compared to monotherapy	0.820	[174]
Probabilities of virginal breeding events of tamoxifen	0.091	[195]
Probabilities of virginal breeding events of letrozole	0.042	[195]
Transitional probability of dying with breast cancer progression	0.394	[196]

Docetaxel model: Docetaxel as the chemotherapy for NSCLC, the search terms were Carcinoma, Non-Small-Cell Lung [MeSH Terms] AND docetaxel AND best supportive care. The identified parameters show in Table 6.6. As meta-analysis was not found, I used parameters of transitional probability from single studies instead. The transitional probabilities to prevent disease progression and dying of docetaxel at 0.203 and 0.63, respectively, were obtained from a randomise control trial [175]. In addition, there are common adverse events of the drugs during the treatment period. The yearly probabilities of adverse events occurred for docetaxel contain neutropenia and febrile neutropenia at 0.0673 and 0.018 respectively [175]. As the comparator of docetaxel is the best supportive care, there is no transition probability from treatment responsiveness to disease progression. All patients were assumed to be in the health state of disease progression as there was no treatment for them. The transitional probability of dying among patients after disease progression at 0.89 was obtained from the RCT study in a different country, as there is no evidence in Thailand [175].

Table 6. 6 Treatment effect parameters of docetaxel and its comparator

Parameters	Mean	Reference
Transitional probability of progression of docetaxel	0.203	[175]
Transitional probability of dying of docetaxel	0.630	[175]
Probabilities of neutropenia events of docetaxel	0.0673	[175]
Probabilities of febrile neutropenia events of docetaxel	0.018	[175]
Transitional probability of dying from best supportive care	0.890	[175]

6.2.4.2 Age-specific background mortality of the Thai general population:

It is noteworthy that moving to the final health state (death) might be or might not be related to the disease of interest since patients could die from other causes, such as accidents or other diseases. Age-specific data on the probability of dying for the Thai general population were taken from the Thai Working Group on Burden of Disease and Injuries report [197] (Table 6.7). However, each model has different groups of patients. The starting ages of yearly probability of patients using different drugs were: efavirenz and LPV/r for HIV/AIDS patients at the age of 30 years; clopidogrel for primary stroke patients; letrozole for postmenopausal patients, and docetaxel for patients with the advanced stage of NSCLC, all at the age of 60 years.

Table 6.7 Age-specific probability of dying in Thai general population

Parameters	Mean
Yearly probability for age 0 yr	0.012076
Yearly probability for age 1-4 yr	0.000380
Yearly probability for age 5-9 yr	0.000580
Yearly probability for age 10-14 yr	0.000610
Yearly probability for age 15-19 yr	0.001499
Yearly probability for age 20-24 yr	0.001828
Yearly probability for age 25-29 yr	0.002577
Yearly probability for age 30-34 yr	0.003414
Yearly probability for age 35-39 yr	0.004072
Yearly probability for age 40-44 yr	0.004968
Yearly probability for age 45-49 yr	0.006290
Yearly probability for age 50-54 yr	0.008761
Yearly probability for age 55-59 yr	0.012353
Yearly probability for age 60-64 yr	0.017269
Yearly probability for age 65-69 yr	0.026142
Yearly probability for age 70-74 yr	0.042194
Yearly probability for age 75-79 yr	0.066767
Yearly probability for age 80-84 yr	0.124062
Yearly probability for age 85-90 yr	0.204775
Yearly probability for age 90-95 yr	0.300283
Yearly probability for age 95-100 yr	0.395008
Yearly probability for age 100+ yr	0.471076

Sources: Burden of Disease Project in Thailand [197]

6.2.4.3 Treatment costs: There are four main components of costs: costs of the CL and the counterfactual drugs, costs of adverse effects from the drug in question, costs of treatments of disease complications during the treatment period, and costs of treatments if disease progression occurred. The cost parameters came from Thai studies, and all costs were converted to be in the present year of the study by using the Thai consumer price indexes for the price year 2015 [177].

Annual costs of drugs were calculated as the mean procurement price multiplied by the yearly dose of treatment. Drug price data were obtained from the Drug and Medical Supply Information Centre (DMSIC), which is an affiliation of the Ministry of Public Health. The DMSIC is responsible for collecting drug price information from all public hospitals across the country [198]. An average price of each drug reported by hospitals was used to estimate the drug cost. The yearly doses of drugs were determined from the recommended treatment regimens by the national clinical practice guideline of HIV/AIDS, stroke, breast and lung cancers, as shown in Table 6.1.

In addition, treatment costs for the main adverse event of drugs in question and the main complication of the diseases in question were included. All of the adverse events of the drugs and complications of the diseases during treatment periods were assumed to resolve in less than one annual cycle length. This is a conservative assumption that has been used in several studies [199] [200]. For the costs of treatments, if disease progression occurred, data were directly obtained from relevant cost studies. As my study was a comparison of treatment options, cost items, which were approximately identical in the regimens in question such as administration costs of hospitals, and health professional fees were excluded. The parameters for treatment costs for all five medicines are presented below.

Efavirenz model: Average monthly costs for treatments with efavirenz and nevirapine regimens at 1,127 baht and 1,470 baht, respectively, were multiplied by 12 to estimate annual costs. Treatment costs for the main adverse events of ARV treatment containing the events of skin reaction, SJS, hepatitis, hepatotoxicity, and high triglyceride were 536, 4,186, 2,200, 7,538 and 4,467 baht per episode, respectively [189]. The costs were multiplied by probabilities of the adverse event mentioned in the previous section. In addition, treatment costs of disease complications in terms of opportunistic infections of HIV/AIDS during the period of

using efavirenz and nevirapine were 357 and 2,148 bath per year respectively [189]. Finally, costs for treatment during the state of disease progression from ARV first line therapy at 72,233 baht per year was obtained from Leelukkanaveera 2009. This is a cohort study conducted in 16 community hospitals in Thailand. The cost contained treatment costs with second line ARVs of IDV/r regimen base and laboratory tests [190]. The identified parameters are shown in Table 6.8.

Table 6. 8 Cost parameters of efavirenz and its comparator

Parameters of annual costs per patient	Mean	Reference
Cost of nevirapine used for treatment of HIV/AIDS	17,640	[120, 198]
Cost of efavirenz used for treatment of HIV/AIDS	13,521	[120, 198]
Cost for treatment of skin reaction	536	[189]
Cost for treatment of Steven Johnson syndrome	4,186	[189]
Cost for hepatitis treatment	2,200	[189]
Cost for hepatotoxicity treatment	7,538	[189]
Cost for treatment of high triglyceride	4,467	[189]
Cost for disease complications in nevirapine	2,148	[189]
Cost for disease complications in efavirenz	357	[189]
Cost for progression of 1st line ARV treatment	72,233	[190]

LPV/r model: Average monthly cost for treatments with LPV/r and IDV/r regimens at 3,444 baht and 4,107 baht, respectively, were multiplied by 12 to estimate annual costs. The cohort study by Leelukkanaveere described above was also used to estimate ADR costs. Costs for treatment of ADR containing the events of rash, clinical hepatitis and neutropenia as the main adverse events were at 50.3, 179.6 and 1,203 baht respectively per episode [190]. The costs were multiplied by probabilities of the adverse event mentioned in the previous section. For the costs for treatment of disease complications, the cost was assumed to be equal at 1,788 baht per year for both drugs, as only the average cost was provided [190]. After patients had failed to respond the treatment, costs for treatment during the state of disease progression from ARV second line therapy was at 188,825 baht per years. The cost contained costs for treatment with the more advance ARVs of Atazanavir regimen, costs for health care, and laboratory tests [190]. The identified parameters are shown in Table 6.9.

Table 6. 9 Cost parameters of LPV/r and its comparator

Parameters of annual costs per patient	Mean	Reference
Cost of IDV/r used for treatment of HIV/AIDS	49,821	[120, 198]
Cost of LPV/r used for treatment of HIV/AIDS	41,327	[120, 198]
Cost for treatment of rash	50.3	[190]
Cost for treatment of clinical hepatitis	179.6	[190]
Cost for treatment of neutropenia	1,203	[190]
Cost for disease complication in 2 nd line ARVs	1,788	[190]
Cost for progression of 2st line ARV treatment	188,825	[190] [198]

Clopidogrel model: An average costs of clopidogrel 75 mg per day was multiplied by the price of drug at approximately 2 baht per tablet used for 365 days. Average costs for treatments of ticlopidine 200 mg every 12 hours used for 365 days was multiplied by the price of drug at approximately 5 baht per tablet. Costs for treatment of disease complications were excluded because the drugs are used for prevention. An average cost for treatment ADR contains the event of neutropenia at 20,362 baht per episode as the main adverse events [201]. The ADR cost was multiplied by probabilities of the adverse event mentioned in the previous section. Finally, after patients failed to respond the prevention, an average cost for treatment during the disease progression of non-fatal stroke (as the secondary stroke) at 50,979 baht per year was obtained from a Thai cohort study Khiaocharoen, 2012 [201]. This cost contained costs for treatment for stroke with inpatient rehabilitation service in every 4 months. The researcher collected the cost from medical record review from the Nareasuan University hospital [201]. The identified parameters are shown in Table 6.10.

Table 6. 10 Cost parameters of clopidogrel and its comparator

Parameters of annual costs per patient	Mean	Reference
Cost of ticlopidine used for 2 nd prevention	3,879	[198, 202]
Cost of clopidogrel used for 2 nd prevention	730	[198, 202]
Cost for treatment of neutropenia	20,362	[201]
Cost for health care during the progression of stroke	50,979	[201]

Letrozole model: An annual cost for treatments with tamoxifen (20 mg daily) at 3,549 baht was calculated by using the drug price at approximately 9.7 baht per 20mg tablet used daily for 365 days. An annual cost for treatments with letrozole (2.5 mg daily) at 2,847 baht was calculated by using the drug price at approximately 7.8 baht per 2.5 mg tablet used daily for 365 days. The costs were used to estimate costs for treatment by switching therapy for tamoxifen for three years followed by letrozole for two years, or monotherapy of tamoxifen for five years. The main ADR for breast cancer treatment is virginal bleeding, which is required inpatient care. The inpatients care cost was calculated based on relative weights (RW) of Diagnostic Related Groups (DRG). The cost was estimated from the RW of virginal bleeding (2.2163 RW) multiplied by the cost per RW (8,000 baht). In addition, costs for complementary treatment during being on the therapy accounted for 37,357 baht per year [203]. The cost was multiplied by probabilities of the adverse event mentioned in the previous section. Costs for treatment of disease complications during the disease responsiveness accounted for 4,510 baht per year. Costs for treatment during the state of disease progression after patients failed to respond the treatment in question accounted for 91,518 baht per year [203]. The cost information obtained from Limwattananont 2005. The researcher collected costs from a medical record review in Khonkhan University Hospital [203]. The identified parameters are shown in Table 6.11

Table 6. 11 Cost parameters of letrozole and its comparator

Parameters of annual costs per patient	Mean	Reference
Cost of tamoxifen used for treatment of breast cancer	3,549	[186, 198]
Cost of letrozole used for treatment of breast cancer	2,847	[186, 198]
Cost for treatment of virginal bleeding	17,730	[203]
Cost for health care during being on the therapy	37,357	[203]
Cost for health care during the disease responsiveness	4,510	[203]
Cost for health care during the disease progression	91,518	[203]

Docetaxel model: An annual cost for treatments of docetaxel 100 mg /m² every 21 days (1 cycle) for 4 cycles was multiplied by an average price of drug at 2,999 baht per 100mg [186, 198]. A cost for treatment adverse effects of neutropenia was at 1,899 baht per year [204]. The costs were multiplied by probabilities of the adverse event mentioned in the previous section. In addition, costs for health care during the disease responsiveness and disease progression of advanced NSCLC, were obtained from Thai study Thongprasert 2012 [204]. The researcher collected costs by medical record review from Maharaj Nakorn Chiang Mai Hospital. The cost of health care during the disease responsiveness was at 38,210 baht per year [205]. The cost of health care during the disease progression after patients failed to respond the treatment in question was at 59,200 baht per year [205]. This cost contains costs for treatment for malignant pleural effusion, palliative radiation, pain control and nutrition. For the comparator, patients receive the best supportive care, as the docetaxel for NSCLC has no alternative treatments. Although there was no cost in the first year, it was assumed that the disease progressed rapidly and then the patients moved to the health state of disease progressiveness in the next year of model cycle with the costs of 59,200 baht per year [205]. The identified parameters are shown in Table 6.12

Table 6. 12 Cost parameters of docetaxel and its comparator

Parameters of annual costs per patient	Mean	Reference
Cost of docetaxel used for treatment NSCLC	23,988	[186, 198]
Cost for adverse effect treatment of docetaxel	1,899	[204]
Cost for health care during the disease responsiveness	38,210	[205]
Cost for health care during the disease progression (Best supportive care)	59,200	[205]

6.2.5 Number of patients

According to background information of the Thai health system in chapter 3, among the three public health schemes, only patients under the CSMBS have been eligible to access the patented drug. Therefore, the CL policy affects only patients under the UC scheme of NHSO, and the SSS scheme of SSO. The numbers of patients receiving the drugs under CL policy were obtained from secondary data collected by the NHSO and SSO. The NHSO and SSO obtain the data from hospitals across the country. All hospitals that provide the CL drugs have to report the number of patients, drug dosages, and medical care costs to the NHSO and SSO every month in order to disburse health care budgets. I used the total annual number of patients receiving CL drugs to estimate policy implications. After the implementation of CL policy, the number of patients who received the CL drugs during 2007 and 2014 is shown in table 6.13.

Table 6. 13 The number of patients receiving the drug under CL policy

Drugs	2007	2008	2009	2010	2011	2012	2013	2014
Efavirenz	15,582	23,302	29,291	36,623	44,378	51,931	59,918	61,298
LPV/r	N/A	3,889	6,708	10,717	15,111	18,789	21,758	22,259
Clopidogrel	N/A	N/A	2,856	6,683	10,282	5,868	9,048	10,857
Letrozole	N/A	N/A	N/A	1,558	2,629	1,330	1,382	871
Docetaxel	N/A	N/A	264	434	724	1,186	1,192	882

Sources: NHSO and SSO

6.2.6 Data analysis

I employed Markov models to estimate lifetime treatment cost savings. The Markov models were used to simulate the progression of diseases in question. The models were divided into three distinct states (from when patients started the treatment until the patients died) and transitional probabilities were assigned for movement between these states over one year of cycle time period. By attaching estimates of resource use per patient to the states and the transitions in the model, and then running the model over the large number of cycles until reaching the patient's lifetime limit, it is possible to estimate the lifetime costs of the patients receiving the drugs of interest. After obtaining the lifetime costs per patient receiving either the treatment of factual scenario or counter-factual scenario, the costs were multiplied by the total number of patients under the policy. As the costs for treatment with drugs used prior to CL policy were more expensive than those of the CL drugs, the differences between total costs of treatment in factual scenario and counter-factual scenario were the lifetime treatment cost savings.

6.3 Results

In the result section, all costs presented in this section were converted to be in 2015 US\$. The total life-time costs for treatment per patient by efavirenz compared to nevirapine were 24,486 US\$ and 26,605 US\$, respectively (Table 6.14). There were savings from the treatment costs during the responsiveness and progression states at 429 and 1,690 US\$, respectively. The total difference in treatment costs per patient was 2,119 US\$. For the eight-year of CL implementation, the total number of patients receiving the drugs was at 322,323 patients. Lifetime treatment costs saved by around 683 million US\$ (Table 6.15).

Table 6. 14 Life-time costs of treatment during responsiveness and progression per patient receiving NVP and EFV regimens (2015 US\$)

Costs per patient	Nevirapine	Efavirenz	Difference
Costs in responsiveness	3,223	2,793	429
Costs of progression	23,383	21,693	1,690
Total	26,605	24,486	2,119

Table 6. 15 Life-time treatment costs for new patients receiving NVP and EFV regimens (2015 US\$)

The year at the treatments start	Number of new cases	Lifetime costs of the patients		Policy implications
		Nevirapine	Efavirenz	Cost savings
2007	15,582	414,563,555	381,543,304	33,020,251
2008	23,302	619,956,357	570,576,439	49,379,918
2009	29,291	779,295,410	717,224,035	62,071,375
2010	36,623	974,365,362	896,756,541	77,608,821
2011	44,378	1,180,689,349	1,086,646,691	94,042,658
2012	51,931	1,381,639,069	1,271,590,638	110,048,431
2013	59,918	1,594,135,482	1,467,161,577	126,973,905
2014	61,298	1,630,850,776	1,500,952,474	129,898,302
Total	322,323	8,575,495,359	7,892,451,698	683,043,661

The total life-time costs of treatment per patient by LPV/r compared to IDV/r were around 52,151 US\$ and 62,279 US\$, respectively (Table 6.16). There were savings from treatment costs during the responsiveness and progression states at 2,513 and 7,614 US\$, respectively. The total difference in treatment costs per patient was 10,128 US\$. For the eight-year of CL implementation, the total number of patients receiving the drugs was 99,231 patients. Lifetime treatment costs were saved by around 1,005 million US\$ (Table 6.17).

Table 6. 16 Life-time costs of treatment during responsiveness and progression per patient receiving the drugs, IDV/r and LPV/r regimens (2015 US\$)

Costs per patient	IDV/r	LPV/r	Difference
Costs in Responsiveness	12,615	10,102	2,513
Costs of progression	49,664	42,050	7,614
Total	62,279	52,151	10,128

Table 6. 17 Life-time treatment costs for new patients receiving the drugs, IDV/r and LPV/r regimens (2015 US\$)

Years at the treatments start	Number of new cases	Lifetime costs of the patients		Policy implications
		IDV/r	LPV/r	Cost savings
2008	3,889	242,202,980	202,816,827	39,386,153
2009	6,708	417,767,443	349,831,646	67,935,797
2010	10,717	667,443,901	558,906,642	108,537,259
2011	15,111	941,097,769	788,059,930	153,037,839
2012	18,789	1,170,159,882	979,872,809	190,287,073
2013	21,758	1,355,066,194	1,134,710,340	220,355,854
2014	22,259	1,386,267,966	1,160,838,195	225,429,771
Total	99,231	6,180,006,136	5,175,036,389	1,004,969,747

The total life-time costs for treatment per patient by clopidogrel compared to ticlopidine were around 12,517 US\$ and 13,050 US\$, respectively (Table 6.18). There were savings from treatment costs during the responsiveness and progression states at 280 and 254 US\$, respectively. The total difference in treatment costs per patient was 533 US\$. For the six-year of CL implementation, the total number of patients receiving the drugs was of 45,594 patients. Lifetime treatment costs were saved by around 24 million US\$ (Table 6.19).

Table 6. 18 Life-time costs of treatment during responsiveness and progression per patient receiving the drugs, ticlopidine and clopidogrel regimens (2015 US\$)

Costs per patient	ticlopidine	clopidogrel	Difference
Costs in Responsiveness	353	74	280
Costs of progression	12,697	12,443	254
Total	13,050	12,517	533

Table 6. 19 Life-time treatment costs for new patients receiving the drugs, ticlopidine and clopidogrel regimens (2015 US\$)

The years at the treatments start	Number of new cases	Lifetime costs of the patients		Policy implications
		Ticlopidine	Clopidogrel	Cost savings
2009	2,856	37,274,530	35,751,410	1,523,121
2010	6,683	87,215,424	83,651,607	3,563,817
2011	10,282	134,177,576	128,694,780	5,482,796
2012	5,868	76,575,142	73,446,111	3,129,032
2013	9,048	118,076,266	113,251,406	4,824,860
2014	10,857	141,691,520	135,901,687	5,789,832
Total	45,594	595,010,459	570,697,000	24,313,458

The total life-time costs for treatment per patient by switching therapy of tamoxifen and letrozole compared to monotherapy of tamoxifen were around 7,190 US\$ and 7,297 US\$, respectively (Table 6.20). There were savings from treatment costs during the responsiveness and progression states at 22 and 84 US\$ respectively. The total difference of treatment costs per patient was at 107 US\$. For the five-year of CL implementation, the total number of patients receiving the drugs was at 7,770 patients. Life-time treatment costs were saved by around 0.83 million US\$ (Table 6.21).

Table 6. 20 Life-time costs of treatment during responsiveness and progression per patient receiving the monotherapy and switching therapy regimens (2015 US\$)

Costs per patient	Monotherapy	Switching therapy	Difference
Costs in Responsiveness	6,844	6,822	22
Costs of progression	453	369	84
Total	7,297	7,190	107

Table 6. 21 Life-time treatment costs for new patients receiving the monotherapy and switching therapy regimens (2015 US\$)

Year at the treatments start	Number of new cases	Lifetime costs of the patients		Policy implications
		Monotherapy	Switching therapy	Cost savings
2010	1,558	11,369,024	11,202,527	166,496
2011	2,629	19,184,316	18,903,366	280,949
2012	1,330	9,705,264	9,563,133	142,131
2013	1,382	10,084,718	9,937,030	147,688
2014	871	6,355,853	6,262,774	93,080
Total	7,770	56,699,175	55,868,830	830,345

The total life-time costs for treatment per patient by docetaxel compared to the best supportive care (BSC) were around 2,948 US\$ and 3,281 US\$, respectively (Table 6.22). Although there was a cost for treatment during the responsiveness state at 2,165 US\$, the treatment during the progression state could save at 2,499 US\$. The saving of treatment costs per patient was at 334 US\$. For the six-year of CL implementation, the total number of patients receiving the drugs is 4,682 patients. Life-time treatment costs were saved by around 1.56 million US\$ (Table 6.23).

Table 6. 22 Life-time costs of treatment during responsiveness and progression per patient receiving the best supportive (BSC) care and docetaxel regimens (2015 US\$)

Costs per patient	BSC	Docetaxel	Difference
Costs in Responsiveness	-	2,165	- 2,165
Costs of progression	3,281	783	2,499
Total	3,281	2,948	334

Table 6. 23 Life-time treatment costs for new patients receiving the drugs best supportive care and docetaxel regimens (2015 US\$)

Year at the treatments start	Number of new cases	Lifetime costs of the patients		Policy implications
		BSC	Docetaxel	Cost savings
2009	264	866,681	778,516	88,165
2010	434	1,424,771	1,279,833	144,938
2011	724	2,376,421	2,134,674	241,748
2012	1,186	3,890,409	3,494,648	395,762
2013	1,192	3,912,038	3,514,076	397,962
2014	882	2,892,799	2,598,522	294,277
Total	4,682	15,364,278	13,801,308	1,562,971

The comparative benefits per patient in terms of life year gains and lifetime cost savings are seen in Table 6.24. The total life year gained per person was 2.99 years, and life-time cost savings were 13,221 US\$ per person. For the total population of 479,600 patients, the total life-time treatment costs by the five CL drugs compared to its comparators were 15,442 and 13,708 million US\$, respectively (see Table 6.25). It was found that the eight-year of CL implementation, the total life-time treatment costs were saved by around 1,715 million US\$.

Table 6. 24 Comparative benefits per patient in terms of life-year gains and life-time treatment costs across five drugs (2015 US\$)

Year	Comparators		Interventions		Policy implications	
	Life years	Lifetime costs	Life years	Life-time costs	Year gains	Cost savings
Efavirenz	24	26,605	25	24,486	1	2,119
LPV/r	26	62,279	27.5	52,151	1.5	10,128
Clopidogrel	10.8	13,050	11	12,517	0.20	533
Letrozole	16.1	7,297	16.4	7,190	0.31	107
Docetaxel	1.1	3,281	1.4	2,948	0.34	334
Total	78.05	112,809	81.04	99,292	2.99	13,221

Abbreviation: LPV, lopinavir and ritonavir combination;

Table 6. 25 Life-time treatment costs in the total population across five drugs (2015 US\$)

Year	Number of patients	Comparators	Interventions	Policy implications
		Life-time costs	Life-time costs	Cost savings
Efavirenz	322,323	8,575,495,359	7,892,451,698	683,043,661
LPV/r	99,231	6,180,006,136	5,175,036,389	1,004,969,747
Clopidogrel	45,594	595,010,459	570,697,000	24,313,458
Letrozole	7,770	56,699,175	55,868,830	830,345
Docetaxel	4,682	15,364,278	13,801,308	1,562,971
Total	479,600	15,422,575,408	13,707,855,225	1,714,720,182

Abbreviation: LPV, lopinavir and ritonavir combination;

6.4 Discussion and conclusion

In this chapter, lifetime treatment cost savings, resulting from CL implementation, were estimated in five drugs for HIV/AIDS, stroke and cancer. The drugs are: efavirenz, lopinavir and ritonavir combination (LPV/r), clopidogrel, letrozole and docetaxel. Markov models were employed to predict lifetime treatment cost savings using CL drugs compared to alternatives. Comparative benefits across different drug types were used to identify the key parameters, which should be incorporated in the drug selection criteria in order to gain the most benefit from CL implementation. The key parameters affecting policy implications include the number of patients in need of drugs, treatment effects of drugs in question, and drug costs for treatment of diseases in question. Regarding the of lifetime treatment for patients receiving CL drugs from 2007 to 2014, it was found that the second line ARV therapy with LPV/r created the highest cost savings at US\$ 1,005 million, followed by the first-line ARV treatments with efavirenz at US\$ 683 million, and the secondary prevention of stroke with clopidogrel at US\$ 24 million. For the other two drugs, docetaxel used for treatment of lung cancer and letrozole used for treatment of breast cancer, the cost savings were 1.56 and 0.83 million US\$, respectively.

The findings are consistent with previous literature in Thailand. For example, HIV/AIDS and stroke were the leading causes of public health burden, which includes not only the number of patients but also morbidity and mortality of diseases in Thailand. Empirical evidence of the Thai disease burden indicates that HIV/AIDS was the 1st rank for male and the 2nd rank for female, while stroke was the 1st rank for female and the 3rd rank for male. However, using clopidogrel for stroke treatment creates budget savings significantly lower than HIV/AIDS because the other factors (such as comparative treatment effects and costs of drugs compared to its alternatives) affected total budget savings. For cancer drugs, the total cost savings were lower than that of HIV and stroke, because breast cancer and lung cancer were 11th and 18th rank. In addition, letrozole and docetaxel are recommended to be used for specific types of breast and lung cancers. Therefore, one of the key parameters, which could help policy makers to select the drugs for treatment of a certain disease is the national data of disease burden published by the Burden of Disease Department, the International Health Policy Program [206]. In addition, in a comparison of two

cancer drugs, docetaxel saved more treatment costs. The key explanation was that docetaxel had no alternative treatment [186], and without treatment the disease could progress quickly, leading to increased treatment costs through the high cost of treatment when the disease progressed. Therefore, the issue of drugs used for diseases with no alternative treatments is another important factor that should be included in the criteria for drug selection. The criteria were also mentioned in the meeting of health economic working group under the Thai NLEM committee [207].

Previous studies provided explicit parameters for drug selection: (1) the number of patients in need of the drugs, which could be estimated by using epidemiological data of disease prevalence and incidence; (2) the safety and efficacy of the drug, gained by comparing them with available alternatives; (3) the difference in prices between the currently available patented versions and the proposed generics; (4) the remaining period of patent protection of the drug; (5) variations in prescription practices of health care practitioners and the potential for irrational drug use; and (6) the preparedness of streamlined procedures for registration, importation and distribution of generic drugs under CL policy [70].

The findings of my study are consistent with previous suggestions, but add other important factors especially for the first three parameters relevant to the aspects of drugs. It suggests that the drug selection criteria should be adjusted as follows: (1) it should not target only the number of patients, but consider the diseases which are the leading causes of public health burden, because it measures patient numbers as well as morbidity and mortality of the diseases in question; (2) it should not only look at the difference in prices between patented and generic drugs, but rather analyse the difference in total treatment costs between the potential CL drugs and current practices; (3) it should not only select the drug with the highest safety and efficacy profile, but also drugs which are required to treat diseases with no alternative treatments.

Limitations of this study are that the implications of CL policy were evaluated by comparing the lifetime treatment cost of patients in the situation with and without CL policy. However, it is clear that measuring the same person in two different states at the same time is impossible. At any given moment in time, an individual either participated in the program or did not participate. The person

cannot be observed simultaneously in two different states of with and without the CL policy. This is called “the counterfactual problem”: How do we measure what the outcome would have been for participants in the absence of the policy, or if the policy had not been implemented. In the case of my study evaluating implications of CL policy, for instance, it is not possible to construct a counterfactual by creating a control group or a comparison group.

One of the common approaches to deal with the counterfactual problem is comparisons of the outcomes of program participants prior to and subsequent to the introduction of a program (before-and-after, or pre-and-post comparisons). Therefore, in my study, I compared drug regimens recommended by the Thai clinical practice guidelines (CPGs) before and after CL was implemented for the five drugs. I selected the comparators from the drug regimens that the Thai CPGs recommended as the first choice of treatment before CL implementation to be the counterfactual scenarios (baseline comparators). All of the baseline comparators were out of patent protection. After the availability of generic drugs under the CL policy, the drug regimens recommended in the Thai CPGs were changed, and this was set as the factual scenario. I accordingly assumed that outcomes of interest as measured before and after the CL were acceptable to evaluate implications of CL policy.

The numbers of patients receiving the drug were total annual numbers, which were not possible to disaggregate into individual data. Therefore, several assumptions were made in the analysis. First, although there may be drop-off in some patients during the treatment period or recurrent after the treatment may occur in some cases of patients, the data could not be used to identify that patient group. Therefore, it was assumed that all patients received complete drug treatment according to the protocol. Second, in practice, drug regimens may be adjusted by physicians for each patient leading to case-by-case variation in treatment cost. This study used the common regimen suggested by Thai CPGs to calculate an average cost for treatment to all patients. Third, the cost of treatment may vary according to the age of patients. This study used the average age of patients living with each of the diseases in question as the age for all patients in each specific disease. It was assumed that younger patients consuming higher costs would compensate for the lower costs of older patients.

In conclusion, the findings in this chapter could be used to help identify a set of explicit parameters for inclusion in the drug selection criteria within the preliminary framework of CL policy. Comparative costs across different drug types were used to identify key elements, which created the highest cost saving, in order to shape the criteria for CL drug selection. Key elements in the drug selection criteria are: (1) Drugs for treatment of a disease, which is a leading cause of public health burden; (2) Drugs which create the highest difference in treatment cost compared to current practices; (3) Drugs which are required for diseases with no alternative treatment. The revisions of drug selection criteria suggested above could not only promote the transparency of the policy decision process, but also help policy makers and elites to consider which drugs could potentially create the greatest benefits to society.

Chapter 7: The Thai government's performance in implementation of CL policy

7.1 Introduction

The preliminary framework in Chapter 5 required complementary information to strengthen the policy content. While the findings from Chapter 6 were used to strengthen the contents of criteria for drug selection at the decision-making stage, this Chapter aims to strengthen contents at the policy implementation stage through evaluating the policy performance. The objective of this chapter is to evaluate the performance of the Thai government in implementing CL policy in the areas of drug procurement, substitutions of generic drugs for the patented version, and improving drug access improvements. Success or failure in each area of policy implementation was investigated, and key elements affecting CL policy performance were identified in order to develop strategies to improve the policy performance. The findings could help strengthen the policy implementation framework. In this chapter, I evaluated the Thai government's performance in implementing CL policy for the five CL drugs: Efavirenz, LPV/r, clopidogrel, letrozole and docetaxel. The conditions for implementing the policy were different across these five medicines, and these may create different effects on the performance for drug procurement, drug substitution and drug access. The details of each area are as follows.

First, drug procurement performance was evaluated to assess whether the drug supply completely met demand. Drug supply referred to the volume of drug procured by the Government Pharmaceutical Organization (GPO) as the main procurement agency for CL drugs, and drug demand referred to the purchase order from the three public health benefit schemes: the Civil Servants Medical Benefit Scheme (CSMBS), the Social Security Scheme (SSS), and the Universal Coverage (UC). However, the market conditions for each drug differ in terms of the numbers of generic drug suppliers. For example, there are more generic manufacturers in the ARV market than for other drugs. The limited number of generic drug suppliers for clopidogrel, letrozole and docetaxel made it difficult for the GPO to procure enough drugs to completely meet the demand. Therefore, different market conditions among generic drug suppliers of the five CL medicines could create different effects on

drug procurement, and the incomplete supply of CL drugs could reflect an area of improvement for government performance.

Second, The Thai government has sought to build up the practitioners' confidence through quality assurance of CL drugs. Substitution of CL generic drugs for patented versions was evaluated in terms of changes in practitioners' prescribing patterns. Changes in prescribing behavior result from the confidence of practitioners in the quality, safety and effectiveness of CL drugs, and accepting them as substitutes for patented drugs. The quality of efavirenz, LPV/r and clopidogrel are approved by the Thai Food and Drug Administration (FDA), the Department of Medical Science (DMS) and the Government Pharmaceutical Organization (GPO). However, because Thailand lacks the capacity to assure the quality of chemotherapy products, international laboratories assure the quality of letrozole and docetaxel. In this section, the use of CL drugs under CSMBS is the best case for the evaluation, because patented drugs are only reimbursed under the CSMBS scheme and therefore physicians can choose either patented or generic drugs for CSMBS patients. Changes in the proportion of prescriptions for CL generic drugs versus its patented version for patients under CSMBS were evaluated, and the incomplete generic substitution could reflect weak government performance in this area.

Third, the government performance in promoting drug access was evaluated in terms of increased numbers of patients accessing drugs under CL policy. The UC and SSS schemes are the best cases for the evaluation because patients under both schemes paid for the drugs before the CL was implemented. Therefore, implementation of CL policy could improve access to drugs for patients under both schemes. The CL drugs have been monitored to control uses within treatment indications suggested by the CL proposal. This practice is beneficial to not only promote rational drug use, but also prevent over-consumption because of the lower prices of CL drugs. Each drug is monitored differently which may affect drug access. Efavirenz and LPV/r are monitored by the health benefit schemes because ARV drugs are operated within a special ARV treatment program. Letrozole and docetaxel are monitored by the state committee of the National List of Essential Medicines (NLEM) because complicated cancer treatments have been operated as an NLEM programme. As clopidogrel is not operated by any special program, the drug is monitored at health care facilities. Although CL aims to increase drug access for

all patients, the different mechanisms of drug regulation may create different effects on drug access, and incomplete access could reflect an area to improve government performance.

7.2 Methods

Each of the areas of policy performance mentioned above contains two analytical steps. The first step is to evaluate policy performance by comparing actual performance (as factual scenarios) with ideal performance (as counterfactual scenarios), which allows us to consider the implications of defective performance or unanticipated results. In the second step, if there were any unanticipated results from implementing the policy, I evaluated the magnitude of its implications in monetary terms. The magnitudes of implications in each of the three policy areas were used to prioritise areas of performance that the Thai government should improve in order to gain maximum financial benefits of policy implementation.

Data sources on drug procurement, substitution and access were obtained from Thai government departments. I sent formal letters requesting retrieval of the data with clarification of the research objectives. The data were provided by four governmental organisations; the Government Pharmaceutical Organization (GPO), the National Health Security Office (NHSO), the Health Insurance Systems Research Office (HISRO), and the Drug and Medical Supply and Information Centre (DMSIC). Most of retrieved data were from the period of January 2007 to June 2014, except data on the section of drug substitution, which are available only for the period of January 2012 to June 2014. The data sources are shown in figure 7.1 and details of data analysis within each section are provided alongside.

Table 7. 1 Sources of data

Organizations	Data details
Government Pharmaceutical Organization (GPO)	Volumes and prices of generic drugs procured under CL policy and volumes of drug ordered from health benefit schemes.
Health Insurance Systems Research Office (HISRO)	Volumes of patented and generic drugs purchased under the Civil Servants Medical Benefits Scheme (CSMBS).

Organizations	Data details
National Health Security Office (NHSO)	The number of patients who accessed CL drugs under the Universal Coverage (UC) scheme.
Social Security Office (SSO)	The number of patients who accessed CL drugs under the Social Security Scheme (SSS).
Drug and Medical Supply and Information Centre (DMSIC)	Annual prices of patented drugs procured by public hospitals across the country.

7.2.1 Implications of incomplete supply of CL drugs

For the area of drug procurement, the data were analysed at the national level by including all the three public health benefit schemes (CSMBS, SSS and UC). Procurement data were obtained from the Government Pharmaceutical Organization (GPO) as the national drug procurement agency. Performance was evaluated according to whether the GPO drug supply met the national demand of the three schemes. The volume of drug supply (procurement from drug manufacturers) and drug demand (drug purchase order from health benefit schemes) is recorded and maintained real-time by the GPO through the vendor managed inventory (VMI) system. During the eight-year period of CL policy, all CL drugs except LPV/r were supplied by Indian generic drug manufacturers. LPV/r was produced by the GPO through technology transfer from Indian firms. However, when the Indian drug supply was not sufficient to meet demand, further supplies were procured from other sources.

The Thai government's performance in drug procurement was analysed in two steps: (i) whether there was sufficient supply of generic drugs under the CL policy to meet the national demands, and (ii) if an incomplete supply of CL drug occurred, what was the implication. In the period of incomplete supply, the GPO had to purchase drugs from other sources at higher prices than that of CL sources. Therefore, the Thai government had to shoulder the burden by paying higher prices throughout this period. The longer the incomplete supply occurred, the higher the costs of using the more expensive sources of drugs. Implications were estimated in terms of procurement cost differences between using the drugs obtained from other sources and CL sources.

There are two steps of analysis. First, CL drug procurement was analysed to identify the type of drug and any period of incomplete supply. I compared annual volumes of generic CL drug supply (S_i) and annual national demand for drugs (D_i) throughout the CL period. For any incomplete supply of CL drugs, the gaps between the supply and demand reflected the magnitudes of the implications from the incomplete supply in CL drug procurement. Second, the costs of the incomplete supply were estimated by multiplying the magnitudes of the gaps ($D_i - S_i$) by the respective drug price. Average prices of drugs, which were provided by GPO from other sources during the short supply periods ($POts_i$) represented the factual scenario, and average prices of CL drugs ($PCls_i$) represented the counterfactual scenario. The formula to estimate implications in terms of costs of failure in drug procurement is shown below.

$$IDP = (D_i - S_i) \times (PCls_i) - ((D_i - S_i) \times POts_i)$$

IDP: implications of drug procurement due to the cost of over the period of i (year of each drug commencing purchase) to n (year 2014/Q2)

D_i : Annual actual demand under CL policy (in units of milligrams)

S_i : Annual actual supply under CL policy (in units of milligrams)

$POts$: Average prices of drugs from other sources (in units of US\$ per milligrams)

$PCls$: Average prices of generic CL drug (in units of US\$ per milligrams)

7.2.2 Implications of incomplete CL generic drug substitution

As mentioned earlier, this section focuses on the volume of patented drugs substituted by CL generic versions under the CSMBS. It was checked whether generic CL drugs used by practitioners at health care facilities fully substituted its patented versions under the CSMBS. The HISRO monitored the volume of drugs through the drug reimbursement system. The HISRO is a research institute, which plays an important role in monitoring CSMBS's performance. However, there are limitations to the data used in this section. The volume of patented docetaxel is not included in the database because it is an inpatient drug directly reimbursed by the DRG payment mechanism. In addition, only three years of data (from 2012 to 2014 Q2) of patented and generic drug volumes was collected by the HISRO. CL generic substitutions under the CSMBS scheme were analysed in two parts: (i) whether the

patented drugs were fully substituted by their CL generic versions, and (ii) if an incomplete substitution occurred, what was the implication in monetary terms.

There are two steps of analysis. First, government performance in promoting generic drug substitution was analysed through proportions of CL generic within total volumes of the drug prescribed to patients. The gap between the actual use of CL generic drugs (factual scenarios) and the total use of patented and CL generic drugs (counter-factual scenarios) reflected the magnitude of the implications from the incomplete substitutions. Second, the implications in terms of the health care costs arising from incomplete substitutions were evaluated by multiplying the annual difference between use of CL drugs and total use of the drugs (CL and patented drugs) by CSMBS patients (G_{csmbi}) with the average prices of CL generic drugs (P_{CLi}) and patented drugs (P_{Pti}). The formula is shown below.

$$IDS = (G_{csmbi} \times P_{CLi}) - (G_{csmbi} \times P_{Pti})$$

IDS: Implications of drug substitution as the summation of costs over the period of i (year of each drug commencing purchase) to n (year 2014/Q2)

G_{csmbi} : Annual gaps between actual uses of CL drugs and the total actual uses of the drugs (CL and patented drugs) by CSMBS patients (in units of tablet)

P_{CLi} : Average prices per year of CL drugs (in units of US\$/ tablet)

P_{Pti} : Average prices per year of patented drugs used prior to CL (in units of US\$/ tablet)

7.2.3 Implications of incomplete access to CL drugs

This section focuses on the number of patients who accessed CL drugs under the SSS and UC schemes, assessing whether patients numbers under the two schemes matched expectations. Expected numbers of patients in need of the CL drugs were obtained from a previous Thai study conducted in 2011 by HITAP [70]. Data in the HITAP study was estimated by using linear equations based on historical epidemiological data, and adjusted by minimum possibilities of patients receiving the drugs. As these expected data have been accepted by policy makers and stakeholders [70], the data are used as a benchmark of expected number of patients in need of CL drugs. This section was classified into two parts: (i) whether the actual

number of patients receiving the CL drugs matched the expected number of patients in need of the drugs; (ii) if incomplete access occurred, what were the implications.

There are two steps of analysis. First, performance in promoting drug access was evaluated in terms of the increase in patients receiving the drugs after CL was granted. The difference between expected numbers of patients (EP_i) and actual numbers of patients (CP_i) reflected incomplete access as an unanticipated result. Second, the implications of incomplete access were evaluated in monetary terms. For any incomplete access, patients who have not received CL drugs are given alternative drugs recommended in the CPGs, which have higher costs than CL drugs. Therefore, the more incomplete access, the greater the increase in health care costs. To estimate the cost, the annual difference in expected and actual drug access ($EP_i - CP_i$) was multiplied by the difference between treatment costs using CL drugs (CCl_i) and alternative drugs (CA_t_i). The formula to estimate the cost implications of failure to promote drug access is shown below.

$$IDA = (EP_i - CP_i) \times (CCl_i) - (EP_i - CP_i) \times (CA_t_i)$$

IDA: Implications of drug access as the summation of costs over the period of i (year of each drug commencing purchase) to n (year 2014/Q2)

EP: Expected annual numbers of SSS and UC patients who access to the CL drug

CP: Actual annual numbers of SSS and UC patients who access to the CL drug

CCl: Average drug costs of CL drugs, based on regimens suggested by the Thai CPGs (in units of US\$ per patient per year)

CA_t: Average drug costs of alternative drugs used prior to CLs, based on regimens suggested by the Thai CPGs, (in units of US\$ per patient per year)

7.3 Results

7.3.1 Implications of incomplete supply of CL drugs

The volumes of drug procurement under the CL policy are shown in Figures 7.1 to 7.5. The figures show the names of the suppliers that delivered the generic drugs in a certain period of time. The axis on the left-hand side presents the volumes of drug in kilogram supplied under CL policy. According to information from GPO staff, there was over-stock in 2011 of all drugs; therefore, the volumes in 2012 were decreased as there were some remaining drugs from 2011.

Efavirenz for the treatment of HIV/AIDS: The generic efavirenz has been imported in Thailand since 2007 (Figure 7.1). The drug has been supplied by five different Indian generic firms; Ranbaxy Laboratories Ltd, Emcure Pharmaceutical Ltd, Aurobindo Pharma Ltd, Matrix Laboratories Ltd and MyLan Laboratories Ltd. Because of several sources of generic suppliers in the market, the price of efavirenz decreased throughout the period from 28 baht (0.8 US\$) in 2007 to 5 baht (0.14 US\$) in 2014 / per 600mg tablet (82% price decrease).

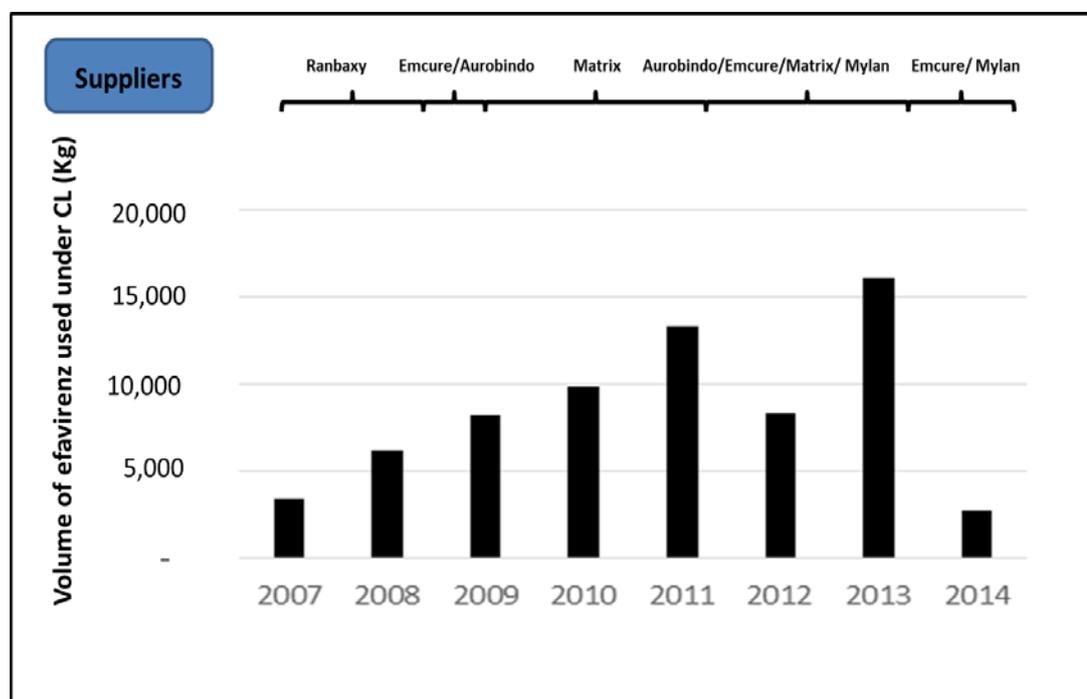


Figure 7. 1 Volume of generic efavirenz drugs and its suppliers

Lopinavir and ritonavir (LPV/r) for the treatment of HIV/AIDS: The generic version of LPV/r has been imported into Thailand since January 2008. In addition, the GPO proposed a strategic plan to obtain technologies transferred from Matrix Laboratories Ltd. to produce a generic version of LPV/r. As a result, although there were limited generic suppliers, the drug demands were satisfied by the locally made generic LPV/r (Figure 7.2). After the drug was locally produced by the government sector, the Indian generic firm decreased the price of its product from 18 (0.51 US\$) in 2008 to 13 baht (0.39 US\$) / 250 mg tablet in 2012 (28% price decrease).

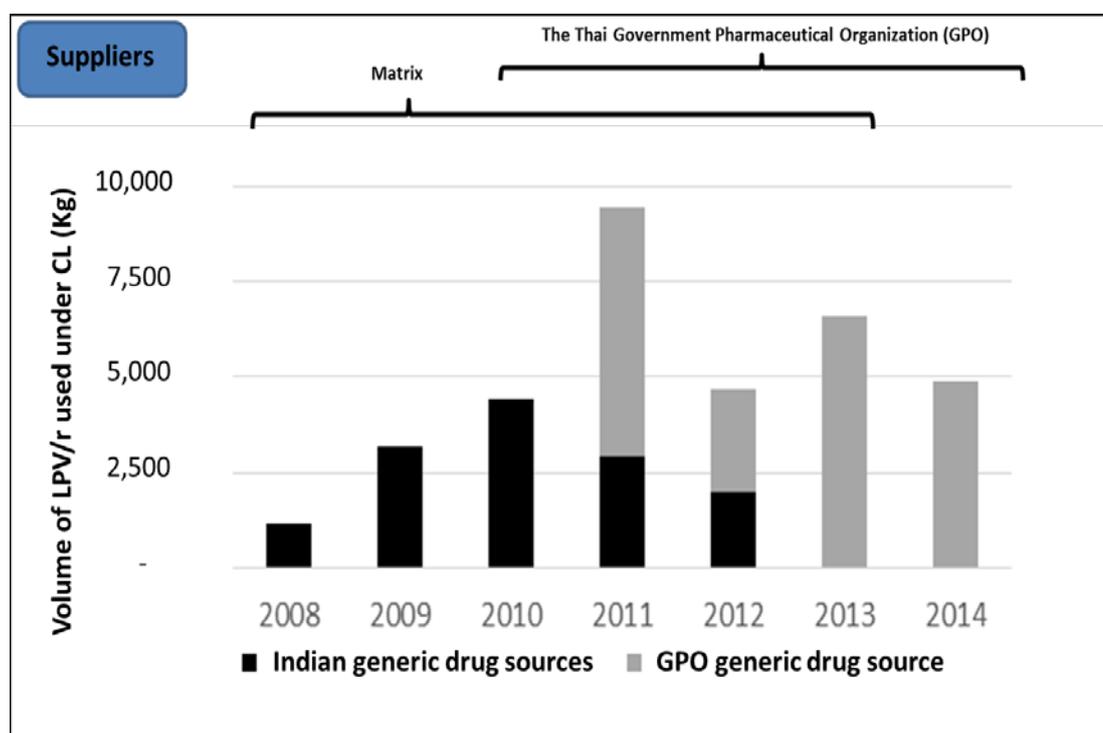


Figure 7. 2 Volumes of generic LPV/r drugs and its suppliers

Clopidogrel for the treatment of cardiovascular disease: The generic clopidogrel has been imported to Thailand since June 2008. However, there has only been a small number of generic suppliers in the market. Moreover, some of the imported generic clopidogrel failed to meet quality standards, and the product was recalled from the market, and that led to incomplete supply to satisfy the drug demand during 2013 to 2014 (See figure 7.3). Consequently, the GPO had to find other sources to maintain the drug supply. During the incomplete supply period, the GPO purchased clopidogrel from another source (Apolets[®]) at the price (15 baht or US\$0.44/ 75mg tablet), which was more expensive than that of the CL source (1 baht or US\$0.31/ 75 mg tablet).

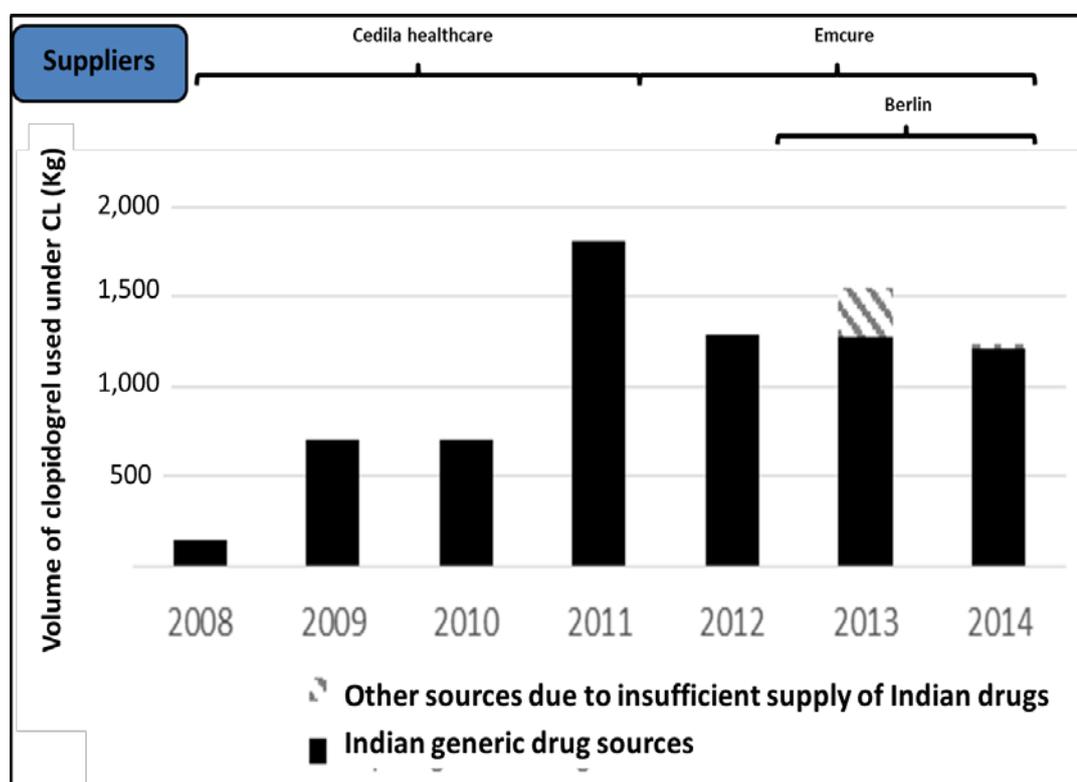


Figure 7. 3 Volumes of generic clopidogrel drugs and its suppliers

Docetaxel for treatment of lung and breast cancer: The implementation of CL policy on docetaxel also had the problems of incomplete supply because generic suppliers did not deliver the drugs in time leading to the country had short supply of the drug during 2010 to 2013 (Figure 7.4). Because of a small number of generic suppliers, docetaxel was substituted by donations from the patented firm (Novartis) through the Taxotere Access Program (TAP) with a condition of donation depending on a proportion of purchase at the normal price of patented drug (1 unit purchased for 5 units donated). Therefore, the GPO had to purchase the patented drug with the normal price, in order to obtain the donations of large volume, and the price per tablet was reduced to around 1,500 baht (US\$154) / 20mg tablet approximately. In addition, during the incomplete supply period, Indian generic firms increased the price of their generic product from 557 baht (US\$50) in 2009 to 981 baht (US\$88) / 20mg tablet in 2014 (76% price increase).

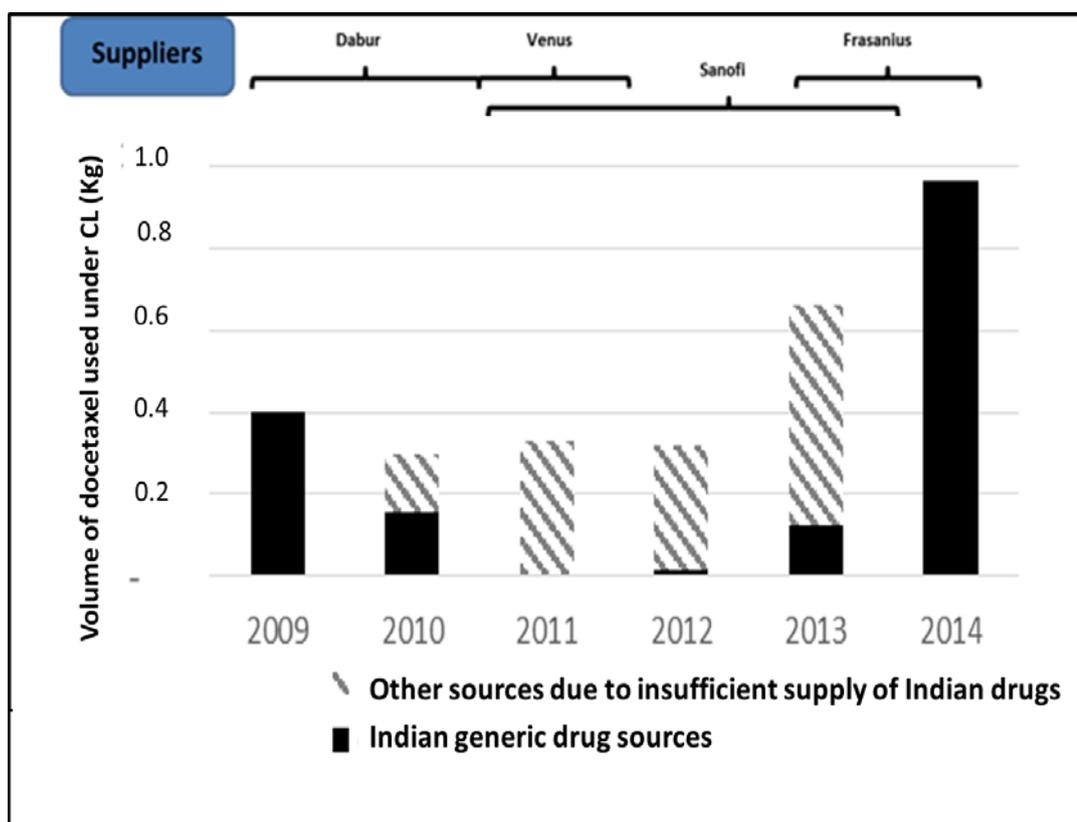


Figure 7. 4 Volumes of generic docetaxel drugs and its suppliers

Letrozole for the treatment of breast cancer: The generic letrozole has been distributed to health care facilities since 2010. Due to a limited number of generic suppliers, the CL implementation was faced with problems of incomplete supply similarly to clopidogrel and docetaxel. The incomplete supply occurred when the generic supplier did not deliver the drugs in time during 2010 to 2012, and GPO had to find other sources of drug supply (Figure 7.5). The generic letrozole was substituted by its patented version with a discounted price from 159 baht (US\$5) to 78 baht (US\$2.3) / 2.5mg tablet. The Indian generic firms increased the price of the generic products from 6 baht (US\$0.18) in 2010 to 12 baht (US\$0.35) in 2014/ 2.5mg tablet (100% price increase).

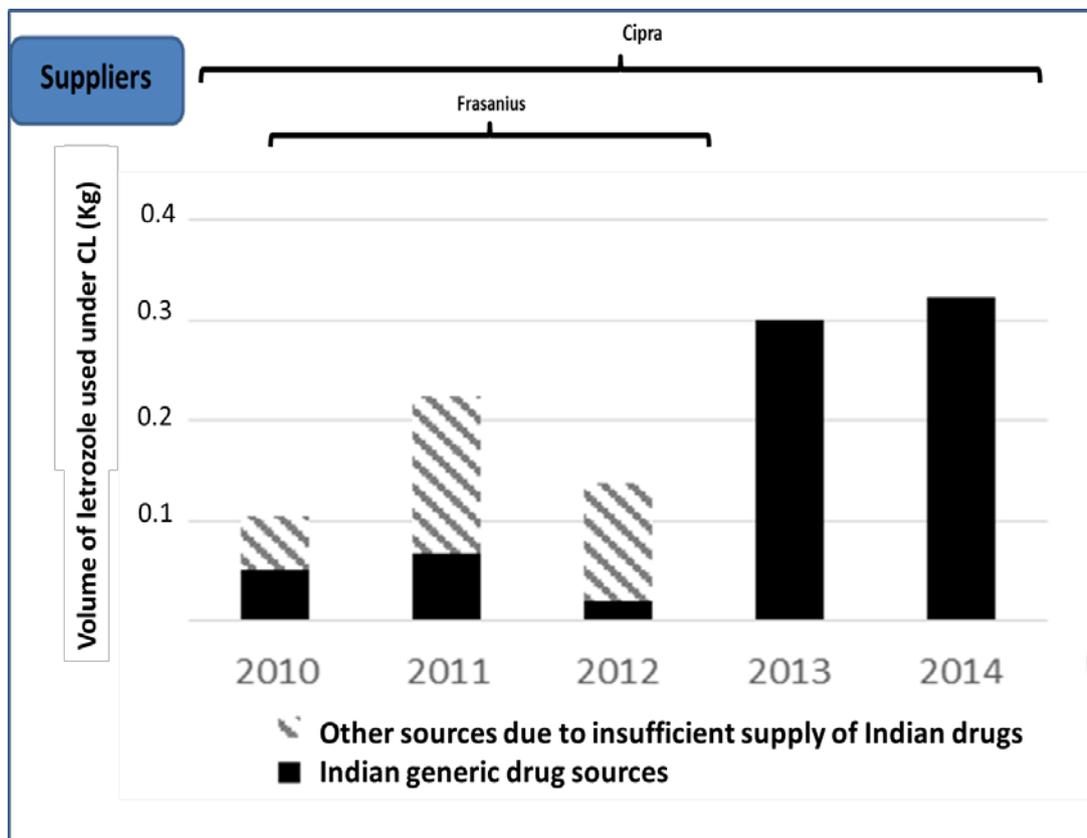


Figure 7. 5 Volumes of generic letrozole drugs and its suppliers

Implications of incomplete supply of drugs

The incomplete supply occurred for clopidogrel during 2013 and 2014, letrozole during 2010 and 2012, and docetaxel during 2010 and 2013. As mentioned above, the generic drugs were obtained from other sources during the period of incomplete supply occurred. In the factual scenario, the actual prices of drugs from the other sources procured by the GPO were used. In the counter-factual scenario, an assumption was made that all patients still received the CL drugs. The table below shows the monetary implications of the incomplete supply. The total differences reflect costs from the incomplete supply of 5.9 million US\$ (Table 7.2).

Table 7. 2 The cost of incomplete supply of drug in US\$ (\$)

	Implication of drug supply	2010	2011	2012	2013	2014 (Q3s)	Total
Counterfactual	clopidogrel only from CL sources				123,425	16,983	140,408
	letrozole only from CL sources	38,607	108,455	88,859			235,921
	docetaxel only from CL sources	91,539	206,963	336,907	592,625		1,228,034
Factual	clopidogrel from the other sources				1,550,318	134,363	1,684,681
	letrozole from the other sources	498,279	1,727,369	1,072,685			3,298,333
	docetaxel from the other sources	280,918	635,153	588,462	1,035,114		2,539,648
Implication	Difference for clopidogrel				1,426,893	117,380	1,544,273
	Difference for letrozole	459,673	1,618,914	983,826			3,062,413
	Difference for docetaxel	189,380	428,190	251,555	442,489		1,311,614
	Total difference	649,052	2,047,104	1,235,380	1,869,382	117,380	5,918,299

Abbreviation: Quarter (Q)

7.3.2. Implication of incomplete drug substitutions

As mentioned in the introduction, this section focuses on the use of drugs under the CSMBS because only this scheme gives freedom to physicians and patients to choose patented or CL drugs for their treatment. The volumes of generic and patented drugs and the percentages of generic substitution to the total use of drugs are shown in Table 7.3. The increasing trends in percentages imply an improvement of practitioner's perception on the quality of CL generic drugs. The proportions of efavirenz, LPV/r and letrozole have continually increased, while that of clopidogrel has fluctuated throughout the three-year period. Although the confidence of practitioners on quality of generic drugs seems to have increased for most of the CL drugs, full-substitution has not been achieved.

Table 7. 3 Outpatient drug reimbursement data in CSMBS

Outpatient drug used under CSMBS	2012	2013	2014 (3Qs)
Volume used of generic efavirenz (tablets)	16.9 x10 ⁷	55.3 x10 ⁷	30.8 x10 ⁷
Volume used of patented efavirenz (tablets)	55.5 x10 ⁷	69.8 x10 ⁷	38.2 x10 ⁷
Percentage of generic to total use	23%	44%	45%
Volume used of generic LPV/r (tablets)	3.2 x10 ⁷	15.9 x10 ⁷	9.8 x10 ⁷
Volume used of patent LPV/r (tablets)	34.7 x10 ⁷	47.1 x10 ⁷	27.4 x10 ⁷
Percentage of generic to total use	9%	25%	26%
Volume used of generic clopidogrel (tablets)	14.5 x10 ⁷	36.3 x10 ⁷	17.5 x10 ⁷
Volume used of patent clopidogrel (tablets)	106.3 x10 ⁷	180.1 x10 ⁷	108.1 x10 ⁷
Percentage of generic to total use	12%	17%	14%
Volume used of generic letrozole (tablets)	0.3 x10 ⁷	0.8 x10 ⁷	1.7 x10 ⁷
Volume used of patent letrozole (tablets)	0.08 x10 ⁷	0.11 x10 ⁷	0.06 x10 ⁷
Percentage of generic to total use	3%	7%	23%

Abbreviation: Quarter (Q); lopinavir and ritonavir combination (LPV/r)

The incomplete drug substitution during 2012 and 2014. As mentioned above, in the factual scenario, the actual prices of patented drugs were used, while in the counter-factual scenario, an assumption was made that all patented uses were substituted by generic drugs and actual prices of generic drugs were used. The costs of incomplete substitution amounted to 119 million US\$ during the three years, as shown in Table 7.4.

Table 7. 4 The cost of incomplete substitution of generic drug in US\$ (\$)

	Implication of drug supply	2012	2013	2014 (Q3s)	Total
Counterfactual	efavirenz with CL drug only	133,429	167,386	91,671	392,486
	LPV/r with CL drug only	496,594	672,314	390,784	1,559,691
	clopidogrel with CL drug only	440,906	840,604	805,809	2,087,319
	letrozole with CL drug only	65,429	139,620	82,101	287,150
Factual	efavirenz with partial patented drug	705,557	887,686	485,821	2,079,064
	LPV/r with partial patented drug	1,019,152	1,584,398	920,978	3,524,528
	clopidogrel with partial patented drug	30,297,646	51,356,766	30,819,820	112,474,232
	letrozole with partial patented drug	1,609,117	2,151,418	1,054,646	4,815,181
Implications	Differences for efavirenz	572,128	720,300	394,150	1,686,578
	Differences for LPV/r	522,558	912,085	530,195	1,964,837
	Differences for clopidogrel	29,856,740	50,516,162	30,014,010	110,386,912
	Differences for letrozole	1,543,688	2,011,798	972,545	4,528,031
	Total differences	32,495,114	54,160,344	31,910,900	118,566,357

Abbreviation: Quarter (Q); lopinavir and ritonavir combination (LPV/r)

7.3.3. Implications of incomplete access

The increase in numbers of patients who accessed the five medicines under CL policy from January 2007 to June 2014 (3 Quarters/ 3Qs) is shown in Figures 7.6 - 7.10. The access is shown in areas under the curve, while the ceiling threshold of expected access obtained from HITAP's study is shown as dotted lines. The expected data of the HITAP's study was estimated by using linear equations based on historical epidemiological data, and adjusted by minimum possibilities of patients receiving the drugs.

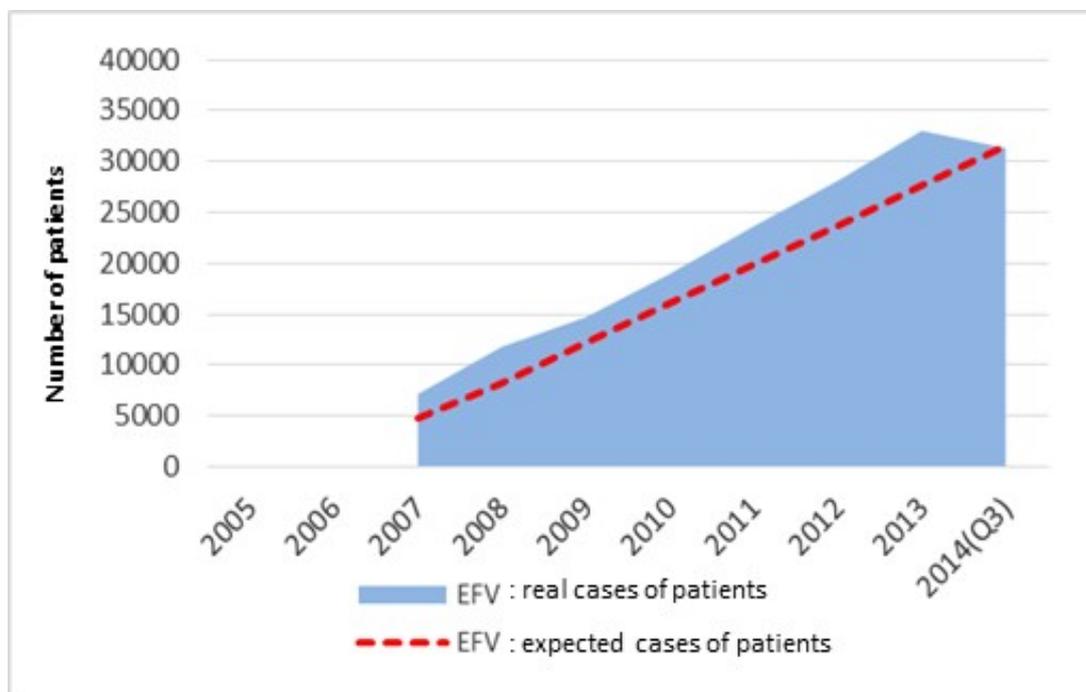


Figure 7. 6 The number of patients receiving efavirenz under CL policy, and the estimation of the expected number of patients receiving the drugs

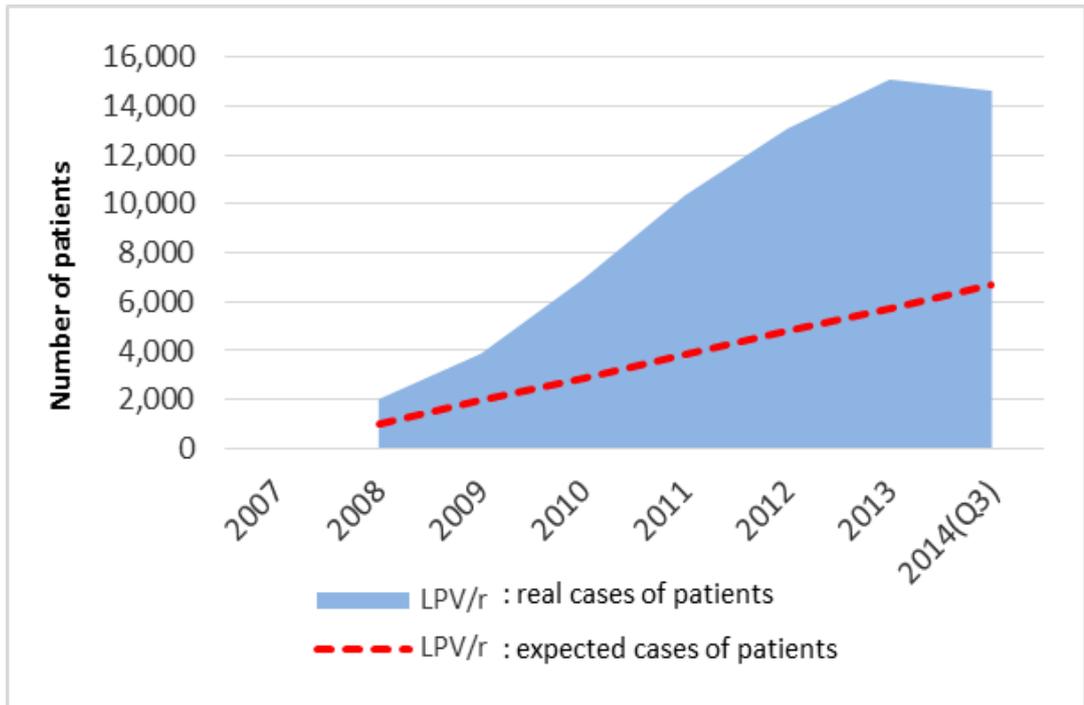


Figure 7. 7 The number of patients receiving LPV/r under CL policy, and the estimation of the expected number of patients receiving the drugs

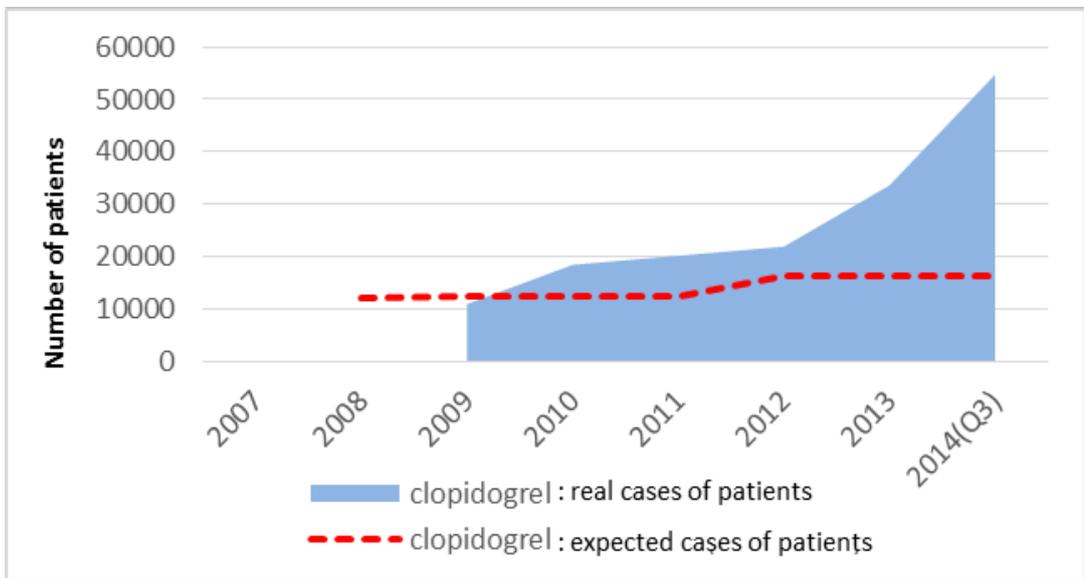


Figure 7. 8 The number of patients receiving clopidogrel under CL policy, and the estimation of the expected number of patients receiving the drugs

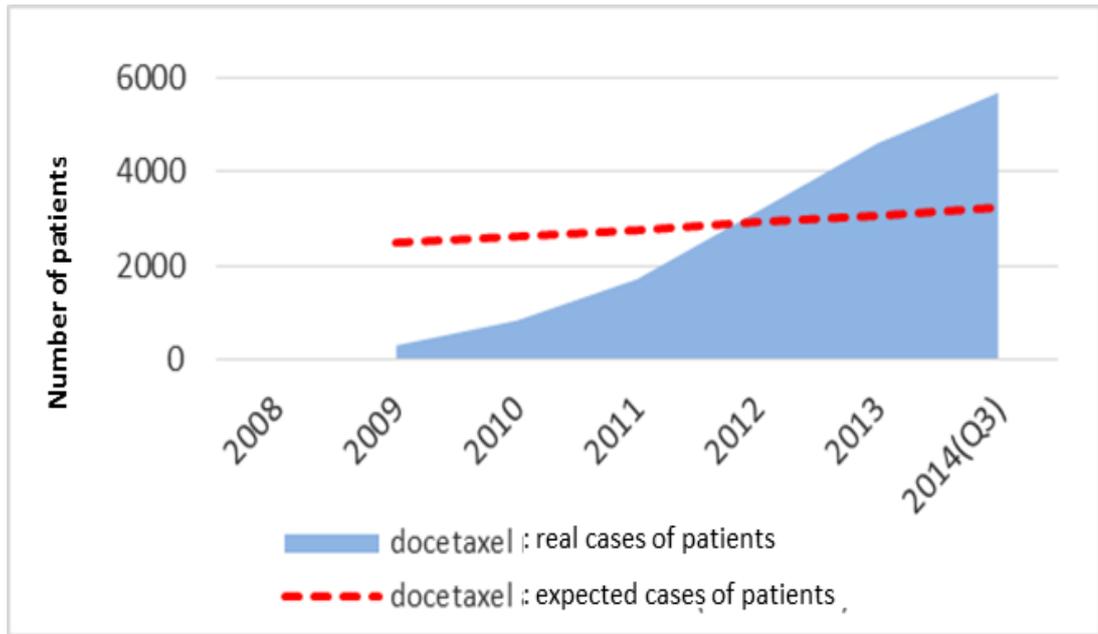


Figure 7. 9 The number of patients receiving docetaxel under CL policy, and the estimation of the expected number of patients receiving the drugs

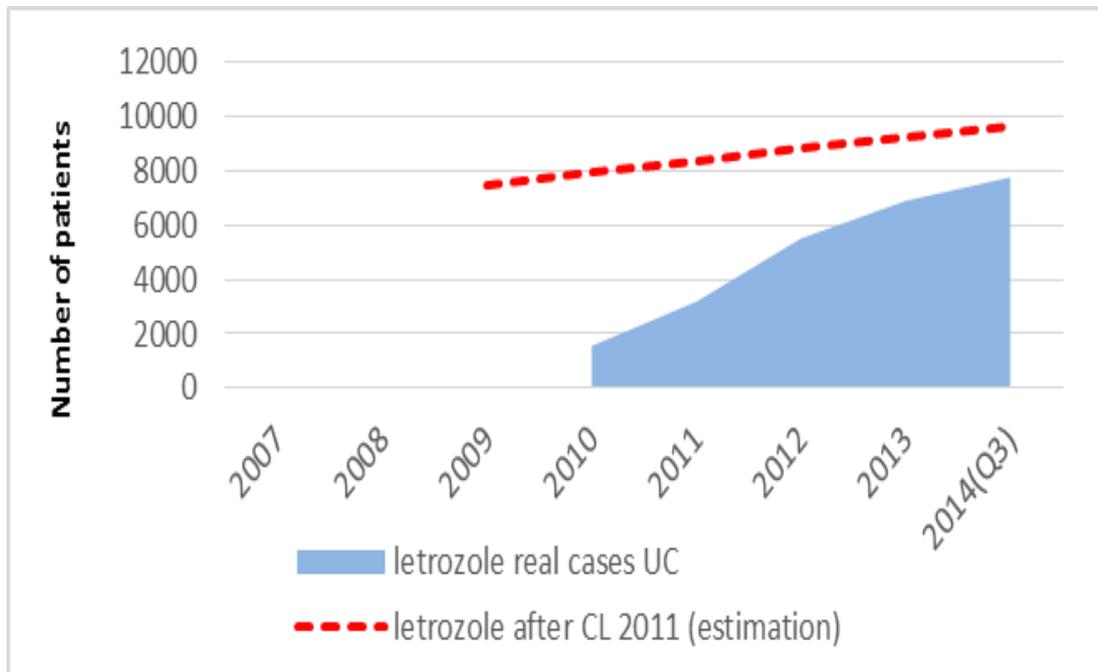


Figure 7. 10 The number of patients receiving letrozole under CL policy, and the estimation of the expected number of patients receiving the drugs

After the Thai government imported generic drugs under the CL policy, the numbers of patients who accessed the drugs have increased in all drugs. As the expectations of drug access were suggested based on minimum possibilities of patients receiving the drugs, it is not surprised that the actual data of drug access exceeded expectation. However, this was not the case for cancer drugs of which regulations were made by the state committee of the National Essential Drug List, as mentioned in the introduction of this chapter. Although the numbers of patients accessing both cancer drugs have been gradually increased, the increasing numbers were more delayed than expectations in the early phase of CL policy implementation. The unanticipated results lead to the costs from the delay in access to cancer drugs during the early phase of CL policy implementation.

Implications of drug access

Implications of the incomplete access to letrozole and docetaxel were analysed. For the factual scenario, the patients in the incomplete access were received the alternative treatments suggested by the Thai CPGs, namely the alternatives of letrozole for treatment breast cancer is tamoxifen, and the alternatives of docetaxel for treatment breast cancer and lung cancer are paclitaxel and palliative care, respectively. In the counter-factual scenario, an assumption was made that all patients who met the indications of the Thai CPGs were received the CL drugs. According to the figures above, the delay in drug access occurred on letrozole during 2009 and 2014, and docetaxel during 2009 and 2011. The cost of the unanticipated results in drug access accounted for 3.6 million US\$ (Table 7.5).

Table 7.5 The cost of incomplete access in patients under UC and SSS in US\$ (\$)

	Implication of drug access	2009	2010	2011	2012	2013	2014(3Qs)	Total
Counter-factual	letrozole with CL drugs	636,005	415,603	266,771	218,682	213,042	166,997	2,049,360
	docetaxel with CL drugs	856,156	702,663	410,392				1,969,211
Factual	letrozole with alternatives	1,678,483	1,096,818	724,002	539,792	326,334	225,435	4,789,799
	docetaxel with alternatives	1,423,162	881,923	515,088				2,820,174
Implications	Difference for letrozole	1,042,478	681,215	457,230	321,110	113,292	58,437	2,740,439
	Difference for docetaxel	567,006	179,260	104,697				850,963
	Total difference	1,609,484	860,475	561,927	336,271	139,158	84,086	3,591,402

Abbreviation: Quarter (Q)

7.4 Discussion and conclusion

As CL policy has been implemented in the country for eight years, the implementation period is sufficiently long to evaluate the Thai government's performance. The evaluations include three areas of policy implementation: drug procurement, drug substitution and drug access, because the three areas sufficiently cover the overall performance of concerned activities from up-stream to down-stream of the supply chain. To evaluate the performance, actual performance (as factual scenarios) with ideal performance (as counterfactual scenarios) were compared to estimate differences between two scenarios; the difference represents the implications of defective performance or unanticipated results. If any unanticipated result in implementing the policy was found, I evaluated the magnitudes of the implications in monetary terms. The findings highlighted the differences in magnitudes of implications across the three areas. Therefore, the findings could be used to help prioritise areas of focus for the Thai government to improve performance. It was found that the highest ranking area of focus was drug substitution, followed by drug procurement and drug access, respectively. However, it is important to use the findings of this study with caution because there are a number of assumptions. The details of each area of focus are provided below.

For the area of drug substitution, estimates were based on an assumption that physicians prescribed CL drugs for all CSMBS patients, and all of the patients were also willing to use the CL drugs. In addition, there are limitations to the data used: firstly, the volume of patented docetaxel is not collected in the database; and secondly, only three years of data (from 2012 to 2014 Q2) on patented and generic drug volumes were available to employ in this analysis. Although the implications in this section are likely to be underestimates compared to other areas, the implications created the highest costs at 119 million US\$, two times higher than other areas. Therefore, improving physician perceptions of the quality of CL drugs should be a key priority for the Thai government. Resolving this issue could result in significant savings for the Thai public health system.

For the area of drug procurement, the implications were evaluated of whether drug procurement by GPO met the national demand. Any gap between the actual

supply and national demand would reflect incomplete supply. During a period of incomplete supply, CL drug demand must be met with drugs from other supply sources. In the counter-factual scenario, it was assumed that CL drugs with the same sources and prices were used to fulfil the incomplete supply. It was found that the implications of incomplete supply created the second highest cost at 5.9 million US\$. Procurement for two ARVs seems to offer an example of success because incomplete supply did not occur, while that for the other three drugs requires improvement because foreign suppliers didn't deliver the drugs on time or the quality of drugs supplied failed to meet acceptable standards. Therefore, the external factor of foreign generic drug suppliers also plays an important role in the success of policy implementation. In addition, as the lesson learnt from the success of LPV/r, one effective strategy is to strengthen local generic drug industries rather than relying only on foreign drug suppliers.

Lastly, the implications of incomplete access to CL drugs created costs of 3.6 million US\$. Numbers of patients under UC and SSS who had access to the drugs were analysed and compared to expected numbers. The gap between the expected and actual number of patients who had access to the drugs would reflect government performance in promoting drug access. An assumption was made in the counter-factual scenario that all patients who met the indications of the Thai CPGs received CL drugs. It was found that, in reality, not all patients who met the indications received the drugs from the beginning of CL policy implementation. Drug access was slower for docetaxel and letrozole than for other drugs. Problems in promoting drug access result from regulation that previously allowed only tertiary hospitals to prescribe the drugs. However, since 2011 the scope of legitimate hospitals has been expanded to qualified secondary hospitals, due to the feedback from health care facilities. The number of patients receiving the drugs consequently has increased in recent years. Therefore, feedback from local health care facilities played an important role in improving CL implications.

In conclusion, there are four elements that should be prioritised and included to strengthen the preliminary framework: (1) strengthening physician' confidence in the quality of CL drugs should be prioritised as vital; (2) reducing interruptions of drug supply from foreign suppliers; (3) strengthening the capacities of local drug

industries to maintain drug supply in the long run; and (4) encouraging policy feedback from local facilities to improve performance and policy implications. These important points could help develop strategies to improve Thai government performance in implementing CL policy.

Chapter 8: An evaluation of the Thai government's performance: qualitative approaches

8.1 Introduction

The preliminary framework was initially developed from generic policy elements proposed by inter-governmental organisations such as the WHO and WTO. This was presented in Chapter 5. The contents of the decision-making process and policy implementation in the preliminary framework were strengthened by using quantitative data on implementation of CL policy in Chapters 6 and Chapter 7, respectively. In chapter 8, the performance of CL policy throughout the process of agenda setting, policy formulation, implementation and monitoring were evaluated by qualitative approaches.

The objective of this chapter is thus to assess the applicability of the framework in Chapter 5 by using qualitative data. Applicability was assessed as to whether the policy elements identified from inter-governmental organisations were consistent with Thai policy elements in implementing CL policy. Any additional policy elements found from the Thai CL experiences, but not mentioned in the preliminary framework, are highlighted in this chapter. Document reviews, semi-structured interviews, and observations of meetings were employed to collect qualitative data. A wide range of data sources from government sectors and non-government sectors were used to ensure that the findings comprehensively represent all key aspects of the CL policy process.

The insights were collected from informants in terms of knowledge or opinion about key elements that influenced the Thai CL policy process. The policy process was classified into four stages: agenda setting, policy formulation, implementation, and monitoring. Therefore, in each stage, the insights collected through interviews contained four aspects of policy elements: policy activities, supportive instruments, contextual factors, and actors. The outline of what key insights I collected through interview is as follows.

- What did contextual elements influence in each stage of CL policy, and did each contextual element create positive or negative influence?; and if any contextual

element having negative influence was found, which approach was used by the former government to deal with the influence?

- Which alternative measures were used by the Thai government to promote drug access, and what were key success factors in implementing each of the measures?
- Which activities were conducted by the Thai government in each stage of CL policy?; and which supportive instruments were used to support each of the activities?
- Were there any obstacles or problems of CL implementation?; and if any obstacles or problems were found, which strategy was used by the former government to overcome them?
- Were there any unanticipated effects of the CL implementation by the former government?; and if any unanticipated effects were found, what was the main cause of the unanticipated effects, and what is the key solution suggested to avoid it in the future?
- What were strengths of the Thai health system that should be maintained to support CL policy; and what were weaknesses or limitations of the Thai health system that should be improved in the future?
- Are there any new ideas or new knowledge that might improve the Thai government's performance in implementing CL policy?
- Who participated in each stage of CL policy?; what was the role of each actor in intervening in the policy process?; did they succeed or fail in intervening in the policy process?; and what was the key factor of their success or failure?

8.2 Data collection and analysis

Document reviews: The aim of the document review was to identify policy elements relevant to the decision making and implementation of drug policy, focusing on CL policy in Thailand. A wide range of published and grey literature, such as journals, study theses, books, conference proceedings, reports, minutes, letters and media reports were purposively reviewed. The inclusion criteria were as follows: all documents mentioning CL policy in Thailand published between 2007 (the first use of Thai CLs) to March 2015, and produced by the sectors concerned as

summarised in Table 8.1. The documents were read to analyse content relevant to CL policy and directions on an appropriate use of the policy in the future. Throughout, the process, the information was examined for its content and the contexts in which it was produced and functioned.

Table 8. 1 The list of documents

Sectors	Types of documents
1. Governmental sectors	Government notifications, statements, official documents, minutes, letters, and reports were obtained from responsible agencies and libraries.
2. Academic sectors	Domestic and international journals, conference proceedings, research reports, study theses, and books were obtained from research institutions and libraries.
3. NGOs	Local and inter-NGO reports, statements, official documents, and books were obtained from responsible agencies and libraries.
4. Private sectors	Local firm or headquarter reports, statements, official documents, and books were obtained from libraries.

Semi-structured interviews: These provided the perspectives of respondents. The interview respondents were purposely selected according to their roles within the process of CL policy decision-making and implementation. Stakeholders were identified from a combination of secondary sources (e.g. meeting reports), and a snowball approach. Semi-structured interviews were used to allow respondents to share their experiences and perceptions of the issue in a free and flexible manner. Five groups of stakeholders were interviewed face to face: (i) government sectors, (ii) academic sectors, (iii) non-profit organisations (NGOs), (iv) private sectors, and (v) health care practitioners. The list of stakeholders is shown in Table 8.2.

Table 8. 2 The list of informants

Sectors	Key informants	No. of informants
1. Governmental sectors [GS]	Government officers from the Ministry of Public Health who participated in the CL policy process.	5
2. Academic sectors [AS]	Academies in the area of access to medicines from universities.	2
3. NGOs [NS]	Non-profit organisations from patient groups including HIV/AIDS, heart disease, and cancer.	2
4. Private sectors [PS]	Executive of the Thai Pharmaceutical Manufacturers Association.	1
5. Health care practitioners [HS]	Health care practitioners in the areas of HIV/AIDS, heart disease, and cancer from health care facilities	3

Key informants were asked for insights into the important elements that led to the implementation of CL in Thailand. The interviews took around 30 minutes for each informant and were held between September 2014 and March 2015. The interviews were conducted and analysed in Thai. Spreadsheets were used to collect information on all interviewees, date and time of interviews, and the interviewee's study IDs. The codes were annotated by a respondent number and their affiliations as from government sectors (GS), academic sectors (AS), NGO sectors (NS), private sectors (PS), and health professionals (HS). Follow-up interviews were conducted with two key informants in order to verify the information.

Observation: I observed four meetings concerning the topic of access to essential medicines in Thailand. The observations were conducted in relevant meetings to collect policy messages concerning the key elements, which influenced the CL policy decisions and implementation in Thailand. The meetings were held between September 2014 and July 2015 to discuss the issue of access to medicines in Thailand. The list of meeting details is shown in Table 8.3.

Table 8. 3 The list of meeting observation

No	Dates	Meetings	Hosting agencies
1.	September 5 th 2014 [OS01]	The HSRI steering committee meeting for advising research under the project of improving capacities for access to medicines (ATM) in Thailand.	Health System Research Institute (HSRI)
2.	October 17 th 2014 [OS02]	The consultation meeting with stakeholders in the area for access to medicines. This considered the preliminary results of my thesis.	Food and Drug Administration (FDA)
3.	November 5 th 2014 [OS03]	The expert meeting for developing national policy recommendations to promote access to essential medicines for Thai citizens.	International Health Policy Program (IHPP)
4.	July 7 and 8 th 2015 [OS04]	The International Trade and Health Conference 2015, Government use of license: revisiting after eight years of implementation.	International Trade and Health Programme (ITH)

All information from different sources (stakeholder interviews, relevant documents and observational notes) was analysed through three steps. The first step was to be familiar with the data sources, by re-reading interview transcription and documents. As I did the transcribing of interviews, I was entirely familiar with all of the data obtained. In the second step, all interview transcripts, relevant documents and observational notes were analysed, and key elements and themes were labelled by codes and short phrases, in order to sort data and generate inputs for the thematic analysis process. A set of initial codes was obtained from the preliminary framework in Chapter 5, while a set of subsequent codes was developed after obtaining new information. Some categories were combined with other categories or split into several categories after revisions and refinements of the category systems. The themes based on the study objectives were set, and the code for each theme was created to facilitate the retrieval. The last step was to map the associations between the theme codes by considering patterns of relationship and seeking explanations for these elements within the data. Triangulation of the data was used to verify information from different sources.

8.3 The framework of CL policy in Thailand

There were two main sections of the initial framework. First, the framework for decision-making contains the stages of agenda setting and policy formulation. Second, the framework for policy implementation contains the stages of policy implementation and monitoring. The key elements in the proposed framework to aid decision-making and implementation of drug policy, focusing on CL policy are presented in Figures 8.1 and 8.2, respectively.

Applicability of the framework for agenda setting and formulation

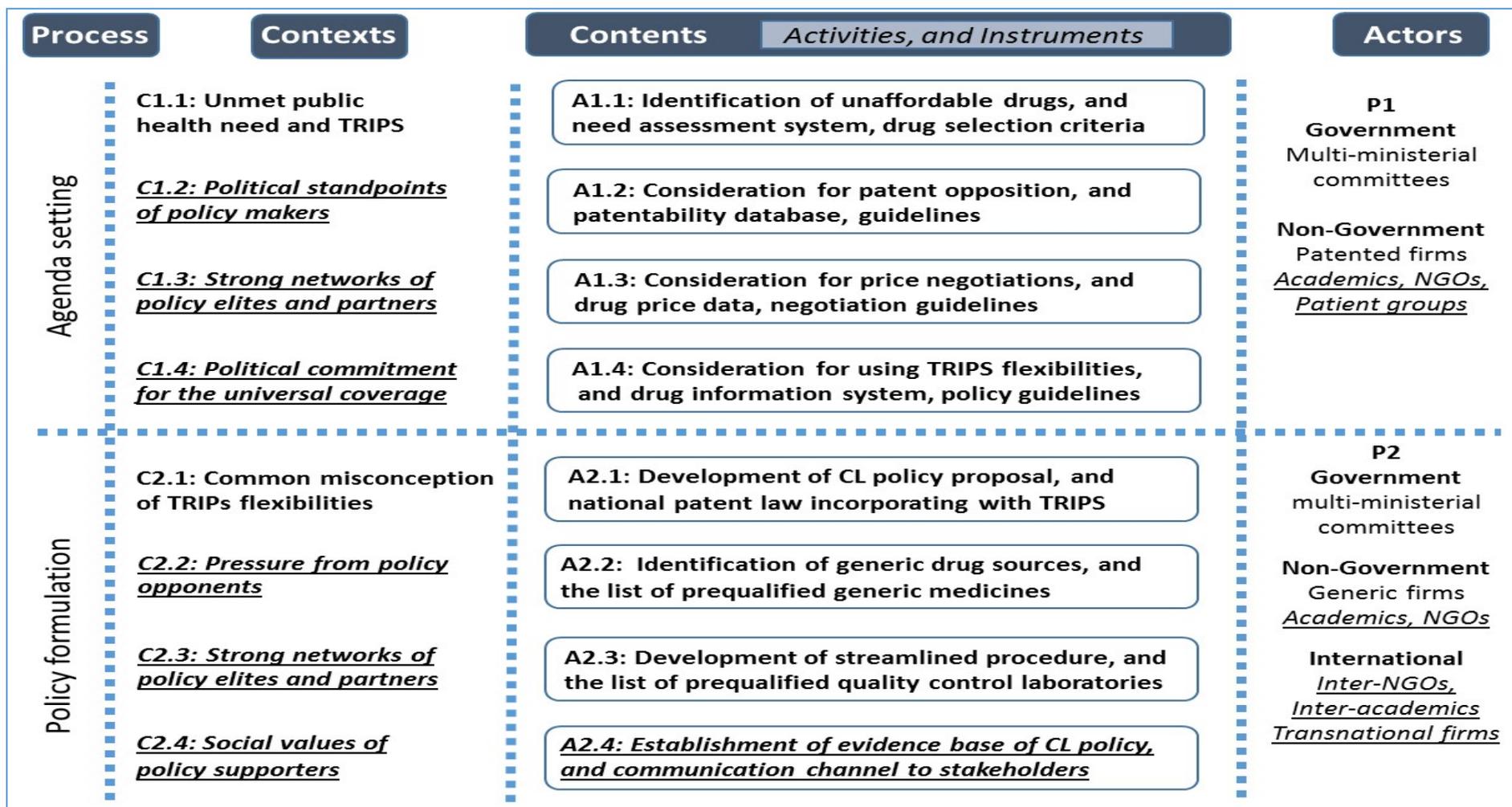
Figure 8.1 shows key elements of the CL policy process in the stages of agenda setting and policy formulation with additional elements arising from experiences of the former government. The preliminary framework in Chapter 5 was strengthened by additional elements identified from the former government's actions and experiences. According to the preliminary framework in Chapter 5, most of the common elements are consistent with the case of Thai CLs. In addition, some further essential elements identified from the Thai experiences were also included in the framework. The additional elements are highlighted in the framework by using underlining and italics.

The first stage in policy process is the agenda setting. Additional elements were identified, including:

- **Three additional contextual elements:** political commitment to universal coverage (C1.2), political standpoints of policy makers (C1.3), and strong networks of policy elites and partners (C1.4).
- **One additional set of actors:** academics, NGOs, and patient groups (P1).

The second stage in policy process is the policy formulation. Additional elements were identified, including:

- **Three additional contextual elements:** transnational drug company reactions (C2.2), social values of policy supporters (C2.3) and strong networks of policy elites and partners (C2.4);
- **One additional activity:** Establishment of evidence base concerning the CL policy (A2.4).
- **One additional set of actors:** academics, NGOs, and transnational firms (P2).



Note: Additional elements identified in this chapter are highlighted by using *underlining and italics*

Figure 8.1 The framework for agenda setting and policy formulation of Thailand

8.3.1 Key elements of agenda setting in Thailand

8.3.1.1 Context in the agenda setting

In the Thai public health system, the main contextual element leading to the decision to issue CL policy was the “**combination of an unmet public health need and the availability of TRIPS flexibilities (C1.1)**”. This is consistent with the preliminary framework in Chapter 5. The Thai government’s white paper clearly mentions that, due to unmet public health needs for essential drugs, the former government raised the issue to the national agenda in order to identify a policy solution. [81, 83]. The details were provided in Chapter 3. Moreover, experiences of the former government also indicated three additional contextual elements as follows.

Political standpoints of policy makers on health over trade interests (C1.2): Among several alternative measures to promote drug access, CL policy, in particular, is associated with conflicts between trade and health interests. The political ideology of Thai policy makers was essential. The former Thai Minister of Public Health who made a decision to issue CL policy addressed that “We don’t have any influence or power; we only have a strong heart to do it for poor people”. (Mongkol Na Songkhla, expressed in [208]:p53). One academic viewpoint mentioned that “the use of CL policy pinpointed the intention of the Thai government to prioritise patient lives over private profits” (Vitaya Kulsoomboon expressed in [88]). The point was consistently addressed that “because the former Health Minister was a strong-minded policy maker who played an important role in protecting public health over commercial interests, he resolutely made a decision to use the CL policy to promote drug access in the country” [208] cited in [209]. It seems clear that the political standpoints of policy makers on public health over trade interests strongly influence the direction of CL policy.

Strong networks of policy elites and partners in agenda setting (C1.3): In the agenda setting stage of the Thai MoPH, multidisciplinary committees were established. The policy elites involved all concerned MoPH departments, such as the Department of Disease Control (DDC), Department of Medical Services (DMS), the

Food and Drug Administration (FDA) and health insurance schemes, which are responsible for dealing with unmet public health needs. In addition, other stakeholders such as medical specialists, NGOs, and representatives from patient groups also played an important role in the stage. A viewpoint from stakeholders also supported that the success of this policy resulted from policy elites who closely worked with the Minister and had strong expertise in political and legal issues concerning CL policy [NS01]. It was consistently mentioned by other informants that strengths of Thai CLs were the involvement of civil society and patient groups because both groups could raise health problems, which seemed to be overlooked by policymakers, while there were strong relationships between domestic and international NGOs, who played an important role in supporting the policy decision [GS03][NS02].

Political commitment to achieve universal coverage (C1.4): The political commitment to achieve the ideological goals of universal coverage is another contextual element that was not included in the preliminary framework. This element played an important role in driving decision makers and policy elites to put CL policy onto the national agenda. The Thai government mentioned in its white paper that the rationale behind the use of CL policy was mainly the mandate to achieve universal access to essential medicine for all Thais [81]. The political commitment to universal coverage was the main grounds used by the MoPH to justify granting CL policy. “Regarding the reason for the MoPH issuing CL policy, the mission of MoPH under the National Health Security Act 2002 is to guarantee access to essential health care treatment for all Thai citizens [...] the MoPH makes its utmost efforts on every feasible measure including CL policy to achieve that committed mission” (Suchart Chongprasert, the representative of the MoPH, expressed in [210]; p5). The Universal Coverage Program was, therefore, an important context influencing the decision to use CL policy. This is supported by an academic study, which stated that “The rights to essential health care, and the responsibility for administration to meet the rightful needs of its citizens, helped to justify the governmental action of introducing the TRIPS flexibilities” [209].

8.3.1.2 Contents in the agenda setting

Identification of unaffordable drugs (A1.1): For the policy content of the Thai agenda setting, the first activity was to identify an unaffordable drug. The Thai government clarified that a decision on whether to issue the CL policy depended on the work of the committee with comprehensive stakeholder involvement and the evidence that they produced [81]. It was clearly mentioned in notifications of the MoPH on the selection of the seven medicines (namely efavirenz, LPV/r, clopidogrel, letrozole, docetaxel, erlotinib and imatinib [211-217]) that the Thai government made an effort to create a transparent process to prioritise high-need medicines in order to solve public health problems [98]. In addition, the Thai government' decisions also largely relied on a system to assess public health needs, which are consistent with the preliminary framework in Chapter 5. A government officer added that the need assessment system is the key supportive instrument for this activity and should be maintained in the long run because it is beneficial for prioritising health problems and selecting a proper drug [GS03]. The issue was raised as part of the national agenda. The revised national drug policy 2011 (BE 2554) included the development of a transparent system to identify inaccessible drugs, which are essential for the public health system [218].

In addition to the need assessment system, this activity required predetermined criteria for drug selection in order to promote transparency and accountability of the policy decision. This is an additional element essential to include in the framework. The seven drugs were selected according to the following criteria [81, 83]:

- Drugs on the National Essential Drug List which are necessary to solve public health problems or use in an emergency/urgency, or use for the management of outbreaks/ epidemics/pandemics, or use for life saving; “and”
- The drug price is too expensive for the government to be able to afford to provide the drugs to beneficiaries of the three main national health insurance schemes to achieve the universal coverage policy.

A Thai study also suggested explicit parameters to be included in the drug selection criteria for issuing CL policy as: the number of patients in need of the drugs (which could be estimated by using epidemiological data of disease prevalence and incidence); the difference in prices between the currently available patented drugs and the proposed generic drugs; the safety and efficacy of the drugs of interest by comparing with their alternatives currently available on the market; variations in prescription practices of health professionals and the potential for irrational use of particular drugs; the remaining duration of term of patent protection of the original drug in question; and other issues concerning the policy process and practices [70]

Consideration for patent opposition (A1.2): As mentioned in Chapters 3 and 5, patent opposition is an alternative measure to overcome the problems of improper patent grants. Rigorous criteria for patentability and implementation guidelines for patent examination are essential to facilitate the process of patent oppositions. However, several viewpoints from government officers indicated that the patentability database for identifying patent status was unstable. For example, even when users keyed in the same search term, the database displayed different results [GS01][PS01]. The situation caused an unanticipated effect in the case of the previous decision of letrozole. The Thai government decided to grant CL for letrozole; however, the patent owner has not yet applied the drug for patent protection in Thailand [GS02]. A study analysing the Thai drug patent system indicated that the problem of the Thai database was not a random but rather a systematic error. It was found that because the system was very complex, only 9% of 88 active ingredients were unable to be verified the patent status [219].

Consideration for price negotiations (A1.3): The second policy option is price negotiation. The MoPH established the committee for price negotiation to promote access to essential patented medicines. Previously, important negotiations with the patent holders had been made on the seven medicines, and details could be classified into three groups. First, for the Lopinavir/Ritonavir (Kaletra[®]) of Abbott Laboratories, the patent owner did not agree with the negotiation and stated that they had gradually lowered the drug prices [98]. Second, price negotiations occurred for the efavirenz (Stocrin[®]) of Merck Sharp & Dome, and letrozole (Femara[®]) of Roche, but the

discounts offered by the patent owners were slight when compared to expected prices of generic drugs with therapeutic equivalence [98]. Third, the patent-owner companies of clopidogrel, docetaxel, and erlotinib reduced drug prices under conditions to offer the drugs for a limited number of patients only [98]. Novartis agreed to provide imatinib for all UC patients under the Glivec[®] International Patient Assistance Program (GIPAP) [83]. Therefore, due to the generous offer of Novartis, CL policy was actually implemented for imatinib. Although in most cases negotiation failed to achieve an agreement, this action enabled the Thai government to avoid using CL for Imatinib.

Consideration for using TRIPS flexibility (A1.4): In addition to negotiation for a price reduction, the committee for negotiation was also responsible for considering the use of TRIPS flexibilities. The MoPH highlighted that in all negotiations, the Thai government attempted to form transparent and constructive relationships with all private firms both before and after the announcement of the policy. However, if negotiations seemed unable to achieve an agreement or public health goal within a reasonable time frame, CL policy was applied. It is noteworthy that as the period of time required for making a policy decision to promote drug access has to be as short as possible in order to satisfy the public health demand, a strategic approach of parallel work was employed by the former government. According to information from a government officer, “patent owners tended to extend the negotiation period in order to delay the implementation of CL policy; therefore, we had to conduct parallel work, negotiating with patented drug firms as well as formulating the policy and preparing the local health system to be ready for implementing the CL policy” [OS04]. This statement was supported by the Thai government’s white paper that “we cannot wait for the results of the discussion and negotiation as we do not want to delay the increase in access to these drugs for our people” [81]. Therefore, the Thai government implemented the strategy in which negotiation and review procedures with patent owners were worked out in parallel to the formulation of CL policy. Although the Thai government wanted to improve efficiency of the decision-making process, primary intention of the Thai government was still to put the most effort to negotiate with patented drug firms, in order to to avoid

unnecessary use of the CL policy. If the negotiations achieved an agreement, the decision to issue CL policy would be terminated.

8.3.1.3 Actors in the agenda setting

For the actors in the stage of agenda setting (P1), the government established multidisciplinary committees to consider essential drugs that were unaffordable due to patent barriers and identify policy solutions to promote access to the drugs. There were two national committees playing an important role in the agenda-setting stage. Both of the committees had multidisciplinary teams consistent with the preliminary framework in Chapter 5.

First, the subcommittee on selecting essential drugs with access problems under the National Health Insurance schemes was established to develop mechanisms for selecting the essential drugs, which are inaccessible for Thai patients. The committee members contained relevant organizations: Affiliation of the Ministry of Public Health (MOPH), including the Food and Drug Administration, the Department of Disease Control, and the Department of Medical Services; Public health insurance schemes, including the National Health Security Office (NHSO), the Social Security Office (SSO), and the Civil Servant Medical Benefit Scheme (CSMBS); Affiliation of the Ministry of Commerce (MOC), including the Department of Intellectual Property; representatives from the Ministry of Foreign Affairs (MFA); representatives from the consortium of Thai medical schools, representatives from patient groups such as the Thai network of people living with HIV/AIDS and cancer care network [220].

Second, the committee on negotiation for patented essential drugs was established to negotiate an affordable price with patented drug firms, using all forms of negotiation including using TRIPS flexibilities. The committee member contains relevant organizations: Affiliation of the Ministry of Public Health (MOPH), including the Food and Drug Administration, the Department of Disease Control, the Department of Health Service Support, the National Health Security Office; Affiliation of the Ministry of Commerce (MOC), including the Department of Internal Trade, the

Department of Trade Negotiations; Affiliation of the Ministry of Foreign Affairs (MFA), including the Department of International Economic Affairs, the Department of Treaties and Legal Affairs; other invited views of the NGOs, academics and individual experts on this issue [221].

The strength of agenda setting in Thailand came through the participation of stakeholders, especially academics, NGOs, and patient groups. The three main groups of actors were added in Figure 8.1. This was an additional factor leading to the success in setting the agenda, and there is an example that shows the role of stakeholders, especially academic groups in directing actions of the government sectors. A study conducted by academics revealed that most patent requests in Thailand (84%) were made in order to grant a patent on an existing drug or on a minor innovative change, and this created significant social costs [222]. In addition, the academic group was initiated in 2011 to develop guidelines for the examination of pharmaceutical patents [223] consistent with the guidelines developed by ICTSD, UNCTAD, and WHO. This academic group played an important role in providing evidence to draw public attention to the problem of low-quality patents in Thailand. Subsequently, the Department of Intellectual Property (DIP) of the MOC published an official document for patent examination guidelines on pharmaceutical products in 2012 [224].

8.3.2 Key elements of CL formulation in Thailand

8.3.2.1 Context in the policy formulation

Common misconceptions of TRIPS flexibilities (C2.1): As mentioned in Chapter 5, a common misconception is that the use of CL is limited to situations of national emergency or other circumstances of extreme urgency; however, the case of public non-commercial is also eligible for CL [146] and cases of Thai CLs confirm this contextual factor. For example, on 13 March 2007, Aumporn Jareansomsak, Country Manager of Abbott Laboratories mentioned that Abbot was disappointed with the infringement of IPRs through CL policy of the Thai government. Abbott decided to withdraw registration of seven new drugs from the Thai market because the decision to issue CL policy had been proceeded with [225]. However, after the Thai government's declarations was made to correct the misconception, Abbott restated the withdrawal because of pressure from policy advocacy [226].

In addition, a number of stakeholders also had the misconception that the Thai government was breaking the law by abusing CL policy for medicines to treat cardiovascular disease and cancer, which were not emergency cases [210]. However, the use of CLs for the drugs is legal when implemented for public non-commercial uses. Therefore, a correct conception and a consistent interpretation should be achieved before implementing CL [210]. This statement was supported by the National Economic and Social Advisory Council that “there should be international cooperation for interpreting the TRIPS flexibilities” [227]. A government officer also made the point that “there is value in developing cooperation among stakeholders including transnational drug industries to settle a consistent interpretation of the TRIP agreement when CL is used on a case by case basis, so as to avoid improper interrupting the use of policy by opponents in the future” [GS04]. Moreover, experiences of the former government also indicated three additional contextual elements as follows.

Pressures of policy opponents (C2.2): In previous cases of Thai CLs, policy opponents attempted to prevent the government from implementing CL policy and to interfere with authorised agencies and the process of policy formulation [98, 228, 229].

This is another element influencing the policy formulation process. Negative responses from opponents of CL policy come mainly from the international sector, including transnational drug companies and HICs which are the home country of patent owners, especially the trade representatives of the USA (USTR) as mentioned in Chapter 2.

In addition, the use of CL policy resulted in conflict with other ministries and domestic industry sectors, which had different interests. One academic indicated that “Ministries have different interests. The Ministry of Foreign Affairs was concerned about the image of our country after getting criticism from high-income countries that Thailand was cheating and stealing other's property [...]. In the same vein, pressure was put on the Ministry of Commerce by local industry sectors” (Vatchareeya Thosanguan as expressed in [230]; p17). In addition, a view of representatives from industry sectors indicated that “the problem started from reactions of the USA on downgrading Thailand from WL to be PWL that would affect the Generalized System of Preferences (GSP) [...] The local industries may be affected by GSP. Therefore, there may be another stream of opponent reactions from domestic industry sectors if CL affects GSP.” (Suthichai Eamcharoenying as expressed in [230]; p10)

Representatives of the patent drug industry, from Merck Sharp & Dohme (MSD), mentioned that “the CL policy may not affect the Thai economy, but it affects the credibility and image of the country as well as confidence in the Thai government. The patent drug industries will not make further research studies in Thailand” (Representatives from MSD as expressed in [226]; p62). Abbot also commented that “the CL policy affected the image of the Thai government with respect to the intellectual property rights and cordiality in negotiation with patent owners (Representatives from Abbot as expressed in [226]; p62).. Novartis supported that “the CL policy destroyed confidence of partners on business, trade, foreign investment and collaboration in the long term” (Representatives from Novartis as expressed in [226]; p62).

Strong networks of policy elites and partners in policy formulation (C2.3):

In response to the previous contextual factor, the structural context of policy elites and

policy supporters was essential to deal with the negative reactions from policy opponents. The policy elite network involved the MOPH, MOC and MFA as well as NGOs, academics and patient groups. The MoPH paid attention to building up a strong network for CL policy. Information from a government officer indicated that “in the first use of CL policy, we didn’t have experience and didn’t invite the Ministry of Commerce and the Ministry of Foreign Affairs to participate in the policy process. However, after we provided the information and opened the floor for other ministries to participate, the reactions from both ministries, which likely objected to the use of CL at the beginning, changed to be more positive for the policy [OS01]. The statement was confirmed by representatives from the Ministry of Foreign Affairs (MOA) and the Ministry of Commerce (MOC) that they recognised the reason why MoPH issued CL policy and did their utmost to help the MoPH to communicate with other sectors [210]. Consequently, the strong network helped in the policy process. “The strong reactions from the USA have been mitigated after justified clarifications were made by concerned ministries and supporters” (Amornsat Singha the representative from MFA expressed in [210]; p9).

The former Thai Minister of Public Health, Mongkol Na Songkhla, made the point that “We got strong supports from stakeholders, both national and international sectors, as never before. We have persistent and capable working groups, including academics and senior government officers who have long experiences with the patent system. In addition, we have good colleagues from other countries and civil society organisations, especially the Knowledge Ecology Institute, Médecins Sans Frontières, Third World Network, Oxfam, Clinton Foundation, etc...Some of them tried to push policy until they themselves were at risk with patented drug industries. Some helped us to seek support from politicians in developed countries such as members of the United States Congress and members of the European Commission as well as international organisations such as World Health Organization. Moreover, the United Nations Program on HIV/AIDS sent letters of support to Thailand. I also heard that the Director-General of WTO made a speech to support the Thai government, and the Head

of the UN Conference on Trade and Development visited Thailand and support the Thai actions.” (Mongkol Na Songkhla expressed in [88]:p57)

Social values of policy supporters (C2.4): The social value of supporting networks was essential to affirming the policy formulation process. The social value of policy supporters was stressed by an academic: “I would earn more money if I worked for transnational drug industries, but I choose to do research to support public health policy because I would like to use my skill and knowledge to help poor people [AS02]. In addition, a view from Thai NGOs highlighted that “It is worth trying even if our work can help only one patient. Our aim is not to use compulsory licensing, but to help patients to get access to essential drugs”. (Nimit Tienudom expressed in [88]; p70). A viewpoint from government officers could be used as a conclusion on the common value of the Thai society. “Even though we are a small country, we tried to protect our rights [...] at the beginning, we believed that we were alone fighting on our own, but when the battle started we had lots of supporters [...] I would like to conclude that all of us have the same concern that patients’ quality of life is the most important issue, not trade or economy”. (Sorachai Jamniendamrongkarn, expressed in [230]; p14-15).

8.3.2.2 Content in the policy formulation

CL proposal development (A2.1): As the first activity in the preliminary framework is the development of the CL proposal, it was found that this activity is consistent with the former government’s action. The government clarified the scope, duration and remuneration of CL policy in compliance with national patent law; and the Thai law also incorporates with the international agreement on TRIPS. It was supported by literature published by Thai academic groups that any country, which aims to grant the CL policy must promulgate its local legal framework as a supportive system in line with the international agreement [231]. Thai patent law shows that the TRIPs agreement article 31 (b) is clearly reflected in the Thai Patent Act. Information from a policy maker indicated that: “we can issue the policy because the Thai law authorises us to do so. I’m admiring the cautious thought of the former lawyers for including the policy in the Thai patent act. However, because no perfect formula for implementing CL policy

was available at the time of Thai CL grants, the Thai government implemented the policy in the way of learning by doing” [OS01]. The issues to be considered in formulating CL policy include: defining authorised agencies, scope of products, duration and target population of drug users, and remuneration of CL policy. The details of CL cases in Thailand are as follows.

For the authorised agency, the Government Pharmaceutical Organization (GPO) has been authorised by the Thai government to produce or import CL drugs and sell these to public health schemes, while profit making is strictly prohibited. If any profit was made, this practice would violate the TRIPs Agreement and the Thai Patent Act, and would pose serious impacts in terms of the law, reputation and image of CLs in Thailand. Therefore, the prices of CL drugs are only based on administrative costs, logistic costs, and other relevant costs of importation or production. [GS02].

For the scope of products under the Thai CLs, notifications of CLs appear to allow the government to exercise the right over a patent, which contains a particular drug in all formulations, including its derivatives patented in Thailand [81, 83]. There are advantages of indicating the scope of product by covering all derivative formulas. For example, in the case of clopidogrel, the Thai government issued CL policy for clopidogrel (Plavix[®]) of Sanofi-Aventis, which was polymorphic form II (Clopidogrel bisulphate form II). However, during 2013-2014, the GPO was unable to find suppliers to provide qualified generic clopidogrel in form II. As a result, the GPO was able to procure clopidogrel (Apolets[®]) from the Berlin Company, which was polymorphic form I, in order to substitute the form II during the period, as allowed by the notification [GS02].

For the scope of target groups of users, notifications of CLs were made that the exercise of the right was limited to patients who were entitled under the universal coverage scheme (UC), the social security scheme (SSS) and the Civil Servant Medical Benefit Scheme (CSMBS) [81, 83]. Information from two stakeholder meetings consistently indicated that such limitation deprived some patient groups who need to use the drugs but were not eligible under the three main public health schemes. For

example, stateless people in Thailand were the most important group ignored by the policy, although most of them were poor and could not afford to access to the said drugs. It was recommended that the Thai government needed to pay more attention to neglected and minority groups of patients in Thailand [OS02], [OS03].

For the duration of CL policy; CL policy can be exercised until the patent expires or there is no more essential need for the drug. A view from informants mentioned that for the cases of ARVs, the notifications of CLs to use the right over patented drugs: efavirenz (Stocrin[®]) of Merck Sharp & Dome and lopinavir/ritonavir (Kaletra[®]) of Abbott Laboratories, were previously indicated the duration for only five years, from 29th November B.E. 2549 (2006) through 31st December B.E. 2554 (2011). However, after the stated period there was still a significant need for the drugs. Therefore, the Thai government had to revise the notification of both ARV drugs by extending the duration until the patent expiration or until the drug was no longer essential to meeting need [GS01]. This practice was also applied for the other CL drugs [81, 83].

Finally, *the remunerations for the use of patent*, the proposal indicated the remuneration under CL policy and clarified the calculation method. Regarding the approach to calculating the royalty rate, although there were several methods proposed by international organisations, the Thai government chose the method mentioned in the document “Use of patented products for international humanitarian purposes” developed by the Minister of Justice under the government of Canada [98]. The government of Canada has strong experiences in using the policy for humanitarian proposes, and they developed a common approach used to calculate the remuneration of royalty rate [98]. The royalty was then adjusted with other LMICs to be 0.5% for ARV drugs, which was consistent with Indonesia issuing CL policy on ARV drugs, and 3% for other drugs as an average rate of CLs in other countries [98]. No evidence was found that patent owners complained about the remuneration rate made by the Thai government.

After developing the CL policy proposal, there are two important movements: First, the GPO **identified sources of generic drugs (A2.2)** as the main procurement agency. The GPO used prequalified generic medicines from the WHO's list of prequalified medicinal products; and the USFDA's list of generic drug approvals. It was noted that directly imported generic drugs from approved manufacturers saved the GPO time and effort in procuring the drugs [GS02]. Second, activity to develop **streamlined implementation procedures for CL policy (A2.3)** was mainly conducted by the Thai FDA on the registration of CL generic drugs. The MoPH invited foreign and domestic manufacturers of these generic drugs to apply for registration in the Thai market in order to be eligible for the procurement stage of implementation [GS01]. According to Thai patent law, even during the stage of formulating CL policy, there is an exemption allowing generic manufacturers to prepare generic drugs in advance for regulatory approval. The registration of CL drugs was accelerated through priority review processes (fast-track registration system) [98]. Although this activity aimed to speed up the registration system and deliver the drugs to patients in need as soon as possible, the accelerating processes firmly maintained the national standard of quality assurance [232, 233]. In addition, it was suggested that generic drug suppliers aiming to apply through the fast-track registration system had to assure the quality of their products from prequalified quality control laboratories [GS01]. These two activities and supportive instruments were consistent with the preliminary framework.

Establishment of evidence base concerning CL policy (A2.4): It's noteworthy that the Thai government establish an evidence base and provide factual information to stakeholders. This is an additional activity initiated by the former government that can be included in the preliminary framework. MoPH policy makers were concerned that information disseminated by policy opponents caused misunderstanding and discredited the MoPH [OS01]. Therefore, the government published two official white papers in order to clarify facts and evidence on the ten key issues related to the government use of patents on ARV, cardiovascular and cancer drugs [81, 83]. It was indicated that the papers were a key policy tool aimed to mobilise support from the public "The stake of this game is very high [...] we are moving into a very dangerous area. We cannot expect

much support from other ministries. Therefore, we have to educate the public; this is why the White paper was publicised.” [234]. In addition, research institutes such as HITAP played an important role in assessing the potential implications. The HITAP study predicted potential health implications and considered economic and social aspects, as mentioned in Chapter 2 [70]. In addition, a number of studies were conducted prior to and during the period of formulation and implementation of the Thai CL policy [68, 70, 71].

This activity required effective communication channels to deliver policy messages concerning historical fact and empirical evidence to stakeholders in the society. A series of activities were conducted by the MoPH and its partners, such as: publishing formal and informal documents to the public; making a speech at national and international meetings; and visiting foreign countries that criticised Thailand’s intentions. In addition, empirical evidence studies were presented to a wide range of stakeholders, for example, meetings of the Thai cabinet [226], and international conferences [235]. This aimed not only to communicate with stakeholder, but also educate other ministries and foreign countries. Eventually, the attempts made by the MoPH and its partners succeeded its aims to make stakeholders understand the purpose of CLs issued by MoPH. This argument was supported by a MOA policy maker that: “I’m glad that the representatives from MoPH, MoC, and MFA are agreed that CL itself is important [...] the negative effect is not as serious as the media mentioned.” (Vitthaya Vechachiva the Permanent Secretary for the MFA expressed in [210]; p13). Information from policy makers supported that evidence-based information played an important role in educating stakeholders and mitigating negative reactions from policy opponents [OS01], [OS02].

8.3.2.3 Actors in the policy formulation

Actors at the policy formulation stage (P2) are similar to the preliminary framework. The Thai government established a multidisciplinary committee called “Sub-committee for Implementing the Government Use of Patent for Patented Essential Drugs”, tasked with developing a CL proposal to exercise the patent rights of the

essential medicines in question and with preparing processes for implementing government use of patent on these drugs. The committee members were mainly affiliated with the Ministry of Public Health (MOPH), including the Food and Drug Administration, the Department of Disease Control, the Department of Medical Services; Affiliates of the Ministry of Commerce (MOC), including the Department of Intellectual Property; representatives from the Office of the Council of State, representatives from the consortium of Thai medical schools, representatives from patient groups such as the Thai network of people living with HIV/AIDS and cancer care network; and other invited views from government offices, NGOs, academics, generic drug industries, and individual experts on this issue [236].

In addition to the transnational drug industries as policy opponents, networks of policy supporters played an important role in dealing with pressure from the opponents. For example, support was provided in the form of evidence-based information from academic sectors such as the Health Intervention and Technology Assessment Program (HITAP), International Health Policy Program (IHPP), Knowledge Ecology Institute (KEI), and the American University program on information justice and intellectual property (Justiceinfo); support in the form of social value such as Médecins Sans Frontières (MSF), Third World Network (TWN), Oxfam, the Clinton Foundation, and the United Nations Program on HIV/AIDS (UNAIDS) [81]. Therefore, these groups of actors were added in Figure 8.1.

The framework for policy implementation and monitoring

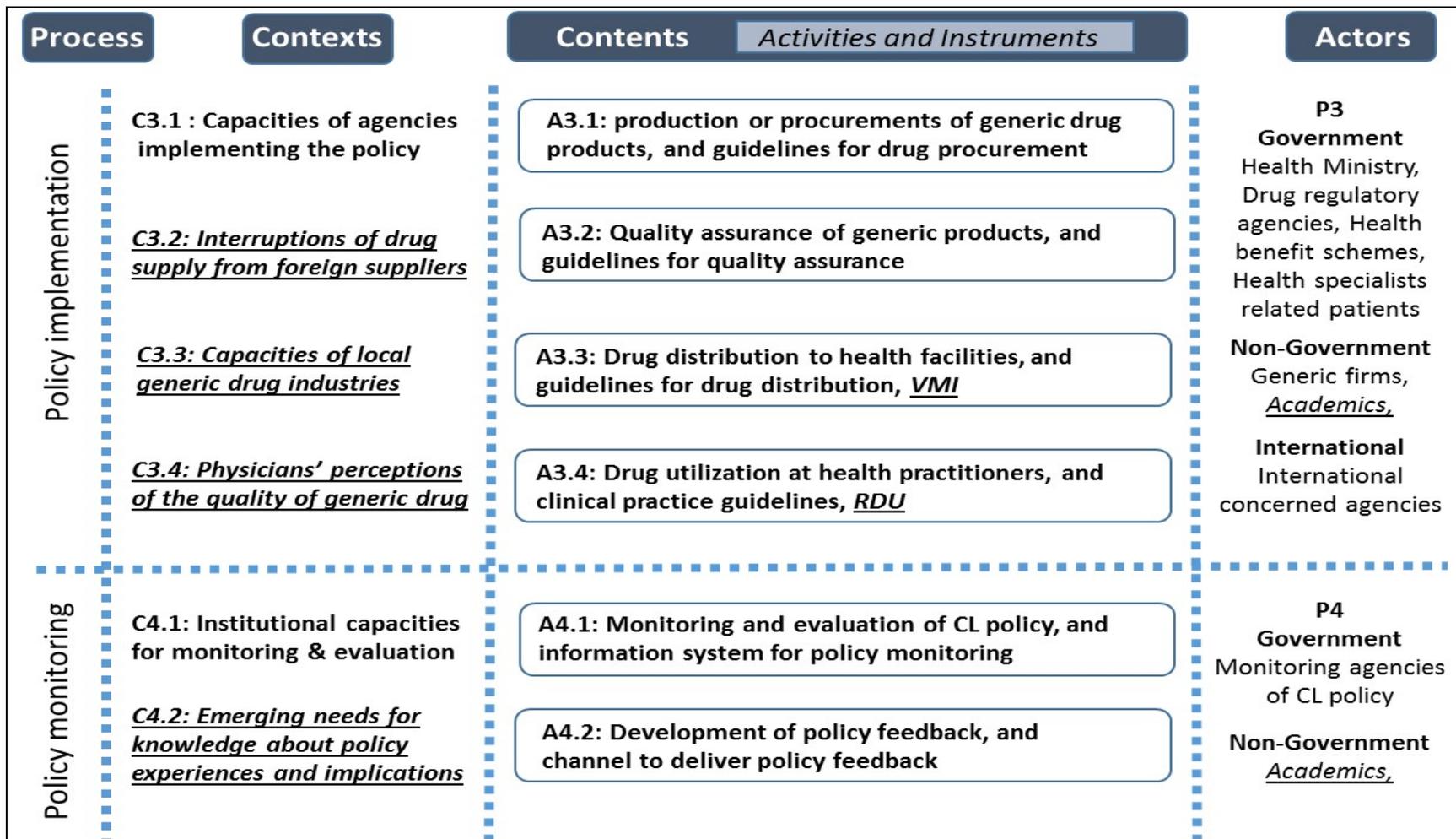
Figure 8.2 below summarises key elements for the implementation of CL policy. The previous section mentioned the stages of agenda setting and policy formulation as the first and second stages of the policy process. This section explains the third and fourth stages in the policy process, namely policy implementation and monitoring. It was found that most elements of the Thai CLs are in the line with the preliminary framework in Chapter 5. The additional elements identified in this chapter are highlighted in the framework with underlined and italic texts. Experiences of the former government suggest additional contextual elements influencing the policy process.

The third stage in policy process is the policy implementation. Additional elements were identified, including:

- **Three additional contextual elements:** unpredictable effects on foreign suppliers (C3.2); capacities of local generic drug industries (C3.3); and physicians' perceptions of the quality of generic drugs (C3.4).
- **One additional group of actors:** academics (P3).

The fourth stage in policy process is the policy monitoring. Additional elements were identified, including:

- **One additional contextual factor:** emerging needs for knowledge about policy experiences and implications (C4.2).
- **One additional group of actors:** academics (P4).



Note: Additional elements identified in this chapter are highlighted by using underlined and italic texts

Figure 8. 2 The framework for policy implementation and monitoring of Thailand

8.3.3 Key elements of CL implementation in Thailand

8.3.3.1 Context of the policy implementation

Capacities of agencies implementing the CL policy (C3.1): Information from interviews consistently indicated that capacities of authorised agencies, which is consistent with the preliminary framework, had an influence on the achievement in the implementation stage. The capacities included personnel qualifications and infrastructures of implementing units. According to the revised national drug policy 2011 (BE 2554), suggested mechanisms are as follows: firstly, strengthening the capacity of local pharmaceutical product manufacturers to supply generic drugs under the policy; secondly, developing quality assurance system of pre-marketing and post-marketing of generic drug products; lastly, reforming the education of health care professionals in medical schools [237]. Moreover, experiences of the former government also indicated three additional contextual elements as follows.

Interruptions of drug supply from foreign suppliers (C3.2): The availability of good quality generic drugs in the market was the key element for the successful implementation of CL policy. As most of the generic drugs procured under Thai CLs have been imported from foreign suppliers, long-term availability and sustainability of foreign generic drugs is an external factor influencing the success of the policy. However, this external factor was not controllable or predictable by import country such as Thailand during the implementation period. A failure in drug supply means danger to patients due to the high risk of developing drug resistance, the high possibility of treatment failure, and the consequent loss of health and economic benefits to the country.

Regarding lessons learnt from experiences of the former government, the cases of clopidogrel, letrozole and docetaxel show evidence that there were interruptions in supply during the implementation period. It was found that the GPO was sometimes unable to find an appropriate generic supplier for the drugs (letrozole and docetaxel during 2011 and 2013; and clopidogrel during 2014). Because the generic suppliers did not always deliver the drugs on time or the quality of drugs supplied failed to meet a proper standard, the GPO had to deal with the unmet need by finding and procuring the drugs from other sources. The GPO and public health

schemes took risks to manage the unanticipated effects from external suppliers as the prices from other sources were higher than the expected procurement plan, and the budget plan had to be abruptly reallocated in order to avoid interrupting the treatments [GS02]. In addition, in the case of erlotinib, information from a government officer indicated that foreign generic manufacturers of erlotinib have not invested their time and resources to conduct quality assurance according to the requirements of the Thai drug registration system. Consequently, the generic version of erlotinib has not yet met the requirements for registration in Thailand [GS05]. Therefore, the external factors of foreign generic suppliers were a serious concern for the government.

Capacity of local generic drug industries (C3.3): The capacity of local pharmaceutical industries was an additional key contextual element essential to support policy implementation. For example, the four drugs under CL policy, namely Efavirenz, Clopidogrel, Letrozole, and Docetaxel, were imported from India after a bidding process. However, a pharmaceutical company could win the bidding a few times, and the next bidding could be won by another pharmaceutical company, which offered different forms of the drug with the same active ingredients [238]. Accordingly, generic drugs obtained from bidding came from many companies, which were different in trade name, pill forms, and packaging. This resulted in problems with drug encoding and recording of patients' drugs administration history, and this was an obstacle to the follow-up of symptoms, therapeutic effectiveness, and undesirable symptoms derived from each drug. More importantly, doctors found difficulties in explaining the reasons for changing the form and figure of drugs, because most patients remembered drugs by their appearance and packaging, especially elderly patients, so alterations resulted in confusion about the medication they were taking [103] [HS02].

Fortunately, the combined drugs of lopinavir and ritonavir (LPV/r) have been mainly produced by the GPO. In this case, no problem occurred because it is easier to manage the locally produced drugs to be produced in the same pill forms and packaging. Hospitals could easily put a code on the drugs and record the patients' drugs administration history, which facilitated doctors' explanations and allowed patients to have a clear understanding of what medication they were taking. It also eased the follow-up of symptoms, therapeutic effectiveness, as well as adverse

symptoms of the drug [103]. This instance could support the argument for strengthening local generic drug industries as this would help simplify that issue with implementation of the policy given the local conditions of the health care system in the country and help avoid the unanticipated effects from foreign drug industries (as mentioned in the previous element) [AS01].

Physicians' perceptions of quality of generic drugs (C3.4): The last additional contextual element was practitioners' perceptions of the quality of generic drugs. There are different contexts across drug types. Practitioners had high confidence in the quality of ARV drugs for treatment of HIV/AIDS because the quality was closely monitored, not only by the Thai FDA as the national agency, but also at health care facilities. As efavirenz and LPV/r are the first and second line of HIV/AIDS treatment, the drugs have commonly been used for all HIV/AIDS patients. In this case, in addition to the quality assurance made by national authorised agencies, physicians at health care facilities themselves had monitored the clinical efficacy and quality of drugs through monitoring CD4 and viral load of patients. (Physician from Mongkutklaw hospital expressed in [226]; p56) This statement was supported by a physician from Kampangsan hospital that "the negative effects of ARVs have not been found, and the efficacy and safety of the drugs have been monitored by the CD4 and viral load in every 6-12 months" [226]. As there were no quality problems raised by physicians on the CL ARVs, confidence in the quality of generic substitution boosted practitioners' willingness to accept, and dedication to do activities under the policy.

However, there was less confidence in generic forms of clopidogrel, letrozole and docetaxel. Under CL, the price of clopidogrel was 98% lower than patented drugs, leading to a constant concern about therapeutic effectiveness. To deal with this situation, academic sectors conducted studies to compare the clinical outcomes of CL generic drugs with its patented version. The details are explained in the section of actors (P3). The empirical academic evidence built trust and confidence among health personnel and patients, and adjusted negative perceptions of the therapeutic efficiency of generic drugs. In addition, there was literature criticising the quality of generic cancer drugs. For example, a study by Vial in 2008 analysed the quality of generic versions of docetaxel in 14 countries and indicated that many generic drugs failed to meet purity standards [239]. The GPO decided to

apply for quality assurance for CL cancer drugs at qualified international laboratories in order to build the confidence of physician groups. [GS02].

8.3.3.2 Contents in the policy implementation

Activities to produce or procure generic CL drugs (A3.1): At the stage of policy implementation, there were a number of activities conducted by the former government. The GPO assessed local capacity whether it needed for technology transfer and investment; availability of technical resources for reverse engineering, costs and duration of developing production processes and product formulations [GS02]. When the local manufacturers had no capacity, the GPO procured the drugs from foreign suppliers. One government officer addressed a lesson learnt from the procurement made by GPO. Because there were a large number of generic suppliers of efavirenz, high competition led to a sufficient supply to meet the demand and a significant decrease in the price of generic products. In the case of LPV/r, the GPO produced the generic products locally to satisfy demand, which in turn brought the price of Indian generic suppliers down. In contrast, due to the limited number of suppliers in the cases of clopidogrel, docetaxel and letrozole, the prices of those three drugs had gradually increased. It was also highlighted that if the market is dominated by a small number of suppliers (oligopoly), they may collaboratively set the price to maximise their profit [GS02]. Therefore, a key success factor was the number of suppliers participating in the bidding process.

Activities to control the quality of generic products (A3.2): On behalf of the MOPH, the Thai FDA is responsible for regulating drugs and stipulates that the quality, effectiveness, and safety of drug registered by the FDA are closely monitored to meet the national standards. Moreover, the Thai FDA developed the procedure protocol for control quality of CL drugs. The protocol suggests that the GPO had to send samples of produced or imported drugs for quality examination at the Department of Medical Sciences (DMSC), affiliated to the MOPH [226]. During 2007 to 2012, there was no evidence that CL products were sub-standard [240]. At the end of 2012, therefore, the DMSC referred its authority for assuring the quality of generic drugs to the GPO to do on its own. However, stakeholders criticised that it was not a good practice because the drugs' quality assurance and monitoring required double-checking by third parties such as DMSC. After the protocol was

changed, evidence showed that CL clopidogrel (which was quality-controlled by the GPO) failed to comply with the national standard, leading to a recall from the Thai market. This point raised serious concerns among physician groups [GS03]. Some viewpoints mentioned that physicians are worried about the quality of CL drugs because of the evidence of sub-standard of CL drugs. (A physician from Nakorn Pathom hospital addressed in [233]; p54). This statement was consistent with physicians from other hospitals that they didn't use the drug under CL policy because of the concern about quality of CL drugs. They had preferred to use other alternative drugs until the quality of CL generic drugs was rigorously approved (A physician from Ratvithi and Chonburi hospitals addressed in [233]; p54-55).

Activity to distribute CL drugs to health facilities (A3.3): The GPO is the main organisation distributing CL drugs according to the purchase orders from the three public health schemes. The public health care schemes have to assess their budgets to cover all patients within the target group of CL policy, and respective hospitals have to report the number of patients, protocol guidelines, drug dosages, and medical care costs to these agencies every month [GS03]. It was highlighted from the Thai experiences that, in addition to guidelines for drug distribution, the GPO and NHSO established the Vendor Managed Inventory (VMI) system. The GPO uses the system for collecting and receiving information about drug purchase orders, prescriptions, transportation and distribution of drugs to hospitals. Because the Thai government grants CLs for providing generic drugs only to patients under public health benefit schemes, the VMI has been used to monitor if the product distributes to users beyond the CL policy's declaration [241]. Based on the VMI database, the CL drugs were distributed to health care facilities only under the three health benefit schemes and a leak into other users (such as private sectors) was not detected. Therefore, the VMI has been used as an effective instrument to monitor the performance of CL drug distribution [GS02], and this is an additional instrument essential to include in the preliminary framework.

Activities to utilise the drug at health care facilities (A3.4): The last activity of policy implementation is the utilisation of generic CL drugs at hospital units. The MOPH developed a set of policy guidelines to facilitate health care workers who use the CL drugs. The Thai clinical practice guidelines (CPGs) were

developed by expert committees from MoPH and health care schemes to promote rational drug use including CL drugs [120, 186, 202]. As the prices of CL drugs were much lower than the drug used prior to CL implementation, this may lead to overutilization of the drugs, especially clopidogrel which has a high proclivity toward variation in practice. A physician indicated that “the CL policy significantly reduced drug prices and could induce the drug utilisation.” (Physician from Chulalongkorn University Hospital expressed in [226]; p36). Moreover, the MoPH also published policy notifications, which were used as procedure protocols of CL drug utilisation. In general, the procedure protocols for different hospitals are similar, as all are based on the MOPH’s Notification. Each of the hospital directors applies the protocol guidelines for dispensing drugs for patients.

In addition, a systematic compliance inspection for the Rational Drug Use (RDU) is required at this stage in the form of utilisation review measures, such as a formation of contracted provider networks, pre/post authorization for specific treatment, and auditing system through inspections of medical records and claim audit [242]. This is an additional instrument suggested by experiences of the former government. As mentioned in Chapter 3, there are two groups of auditors to monitor the drug utilisation: external auditors from the three public health insurance schemes and internal auditors from authorised local hospital staff. It was indicated that the auditing system was developed to monitor the compliance of practitioners’ prescribing performance with the procedure protocols and CPGs, in order to promote rational drug use and avoid over-utilizing CL drugs. [GS03], and this is also an additional instrument essential to include in the preliminary framework.

8.3.3.3 Actors in the policy implementation

For the actors at the policy implementation stage (P3), all the way through these processes, the government established a multidisciplinary team for implementing CL policy. The concerned organizations are affiliates of the Ministry of Public Health (MOPH), including the Food and Drug Administration (FDA) who regulate and control quality of generic CL drugs, the Government Pharmaceutical Organization (GPO) as the drug procurement agency, the Department of Medical Sciences (DMSC) playing the role in assuring quality of medicines, the three main

public health care scheme (NHSO, SSO, CSMBS), and health care facilities across the countries who utilise the drugs.

In addition to the authorised governmental agencies that implement the CL policy, academics who played an important role in promoting stakeholder confidence in the quality of generic drug under CL policy were added in figure 8.2. An academic network in the social research institute in Chulalongkorn University published a series of literature to boost public confidence in the quality of generic drugs including those under CL policy.

There were studies conducted to analyse clinical outcomes of CL clopidogrel in nine tertiary hospitals [243]. In addition, another clinical research study from Khonkaen University compared the efficacy of generic and patented clopidogrel [244]. Both studies concluded that there was no difference in the clinical outcomes between the generic and patented clopidogrel. So the CL generics were suggested as substitutes for the expensive patented drugs because they offered adequate efficacy and value for money. This information was disseminated to health care practitioners who had requested empirical evidence about therapeutic effects of CL generics compared to patented drugs. This is another strong role of academics in the stage of policy implementation, in addition to the authorised governmental agencies under the MoPH, to boost and promote public confidence in the quality of generic drugs under CL policy.

8.3.4 Key elements of CL monitoring in Thailand

8.3.4.1 Context of policy monitoring

The main contextual elements in the process of policy monitoring, which is consistent with the preliminary framework in Chapter 5, is **institutional capacities to monitor performance and evaluate implications (C4.1)**. Information from government officers consistently indicated that, in general, the responsible agencies by itself were monitored their performance. Responsible agencies had to make plans to achieve their objectives, and adjust their behaviours when objectives were not achieved [GS02], [GS03]. Moreover, the output of each responsible agency, as a piece of jigsaw, had to link together in order to create the overall intended outcomes

and impacts [GS03]. The policy was implemented in parallel with monitoring of policy performance, and implications were evaluated at the end.

Emerging needs for knowledge about policy experiences and implications (C4.2): As CL policy has been successfully used by a few countries, there is value of knowledge and experiences of the former government of Thailand in implementing the policy. The information obtained from policy monitoring and evaluation not only helps authorised agencies to improve policy performance, but also enables other stakeholders to understand and learn from cases of CL policy. This is an additional element essential to include in the framework. As this is the first use of CL policy in Thailand, in the meeting of the Thai Cabinet (19 January 2010), the MoPH was assigned to establish systems to monitor and evaluate CL policy. The system had to show the progress of policy performance, the achievement of policy aims, and problems and obstacles to policy implementation, in order to provide feedback to concerned sectors. In addition, as there was a need to enhance stakeholder knowledge of CL policy implications at both national and international levels, it was suggested that the Thai government should publicly report the policy implications on drug access after Thai CLs were granted [233]. A view from meeting participants indicated that other countries would like to learn from the experiences of Thailand [OS04]. A government office informant supported this view, suggesting that the findings of policy monitoring and evaluation could identify the problems, obstacles, and defects arising from the policy, as well as offer strategies to improve the efficiency and effectiveness of policy. This information could help other countries aiming to issue CL to avoid the unanticipated effects occurred in the Thai case [GS03].

8.3.4.2 Contents of the policy monitoring and evaluation

In this process, **activities to monitor performance and evaluate implications of CL policy (A4.1)** are an important step, which is consistent with the preliminary framework, to provide evidence and information to policy makers for making a decision to proceed with and improve the policy, or discontinue it. The activity required a monitoring system to gather inputs and outputs produced by the policy. This system was beneficial not only to monitor policy performance, but also

evaluate policy outputs and outcomes [70]. The scope of works for the former government contains two sections as follows:

(1) Compliance with the policy proposal: the aim of this activity was to monitor the performance of authorised agencies, whether the policy was performed in compliance with the scope defined in the policy proposal, and the achievement of policy objectives as committed to the government in the formal notification of CL policy. The areas being monitored by responsible agencies were as follows: certain product types under the CLs which limit to the CL drugs in all formulations, including its derivatives patented in Thailand; certain population groups which limit to patients entitled persons under the three public health schemes UC, SSS and CSMBS; a certain duration of policy which limits to the defined period of the government notifications; and an achievement in increasing the number of patients who access CL drugs as the main objective of CL policy [GS03] .

(2) Implications of policy: the aim of this activity was to evaluate the CL policy implications. For the former government's actions, both positive and negative implications were evaluated: negative aspects included reactions from policy opponents (withdrawing or delaying registrations of new pharmaceutical products in the Thai market, and objections to the Thai government through political retaliation and economic sanctions); positive aspects included the health benefits from the increase in drug access among patients in need. The benefits for health were presented explicitly in terms of short-term and long-term of national health expenditures, which have been and are predicted to be reduced by the CL policy. The negative implications were evaluated in a previous study in 2013 [71], while short and long term positive implications were evaluated in my study.

According to the preliminary framework, **activities to develop policy feedback to improve policy performance (A4.2)** were consistently suggested by the former government as the final step, in order to translate the empirical data into policy messages for decision makers and other stakeholders in the policy processes. Channels to deliver policy messages were an essential instrument to convey policy messages to policy makers and stakeholders. This required packaging, communication and dissemination of the policy messages in different formats and languages, which were accessible to each audience: policy makers, senior-level

government officers (policy elites), junior-level of government officers (operating staff), academic sectors, advocacy or NGO groups, practitioners in healthcare facilities, patient groups, and the general population [GS03]. It was highlighted that there were misunderstandings between central agencies and local health facilities, and it was therefore suggested that the MOPH should set up the coordination and consultation centre for the CL policy, which was equipped with experts to answer questions and provide essential information about this policy in a timely manner. This could lessen problems relating the policy implementation and bring about trust and confidence among concerned actors in each stage of the policy processes [HS01][HS03].

8.3.4.3 Actors in policy monitoring and evaluation

For the actors in the policy monitoring stage (P4), authorised agencies in the implementation process have self-monitored their performance. As mentioned in the implementation stage, there are several organizations implementing the policy: the Food and Drug Administration (FDA), the Government Pharmaceutical Organization (GPO), the Department of Medical Sciences (DMS), the three main public health care schemes (NHSO, SSO, CSMBS), and health care facilities across the countries. However, information from informants consistently indicated that authorised implementation agencies have sufficient capacity to monitor its performance, but not to evaluate the policy implications [GS01], [GS03]. A view from government officers indicated that this task could be conducted by academic sectors, which did not have conflicts of interest with the authorised agencies engaged in the policy process. Policy evaluations could identify policy suggestions to improve performance of authorized agencies for each stage along the policy process: agenda setting, policy formulation and implementation [GS03].

In Thailand, the academic sector plays an important role in providing evidence-based information to stakeholders including other sectors such as MOC affiliates, MFA affiliates, health care professionals, NGOs and patient groups. Academic sectors include the Health Intervention and Technology Assessment Programme (HITAP), the International Health Policy Program (IHPP), the Health System Research Institutes (HSRI), and research institutes in universities, etc. Many

policy evaluations were carried out by these institutions. Therefore, the academic group was added in Figure

8.4 Discussion and conclusion

This chapter aims to assess whether the policy elements in the preliminary framework (Chapter 5) are applicable to the Thai context. To answer this question, three qualitative approaches (document analysis, semi-structured interviews, and meeting observations) were employed to analyze the applicability of the identified policy elements. Other elements not mentioned in the preliminary framework were included in the framework if they influenced the Thai CL process. In this chapter, policy elements mentioned in the preliminary framework defined in Chapter 5 were consistent with the Thai experience of CL policy. In addition, the experiences of the former government suggested additional elements not mentioned in the preliminary framework.

At the agenda setting stage, the common factor is the combination of unmet public health needs (due to drug patent barriers) and the availability of TRIPS flexibilities. However, while many countries, especially LMICs, have faced the problem of unmet needs in their public health system, few countries decided to issue CL policy. It is clear that, beside the unmet public health need, there must be other essential elements leading to the decision to issue CL. The experiences of the former government indicated three additional elements, which are mainly context-specific to Thailand: political standpoints of policy makers on health over trade interests, strong networks of policy partners, and political commitment to achieve universal coverage. These context-specific elements of Thailand significantly influenced the decision to issue CL policy in the country.

At the stage of policy formulation, one of the key contextual elements are the common misconceptions of TRIPS flexibilities, resulting in stakeholders attempt to interrupt the use of CL policy in Thailand, despite CL implementation complying with the TRIPS agreement. Therefore, the availability of TRIPS flexibilities may be not sufficient; the correct and consistent interpretation of stakeholders is also essential. At this stage, additional contextual elements are relevant to two groups of

stakeholders. First, pressure and negative reactions from policy opponent groups create an unsupportive environment in order to prevent the government from implementing CL policy. In the experience of the former government, these opponent reactions were alleviated by strong networks and common social values of policy supporters. Therefore, teamwork between government and non-government organizations could create a third force to enhance government power to resist pressure from policy opponents and help facilitate the implementation of CL policy.

After the decision is made, the next essential is adequate institutional capacity of authorised agencies to implement and monitor the policy performance. Experiences from the former Thai government identified additional contextual factors. First, interruptions of drug supply from foreign suppliers (which endanger patients and the health system) highlight the importance of the government finding more sustainable suppliers. The capacity of local drug industries, as the second factor, should be strengthened to maintain a continuous national drug supply. When the drugs procured and distributed to health care facilities, physicians' perceptions of quality of generic drugs are the third factor that has a significant effect on the success of CL implementation. Finally, the last contextual factor is the emerging need for knowledge about policy experiences and implications. As CL policy has been successfully used by a few countries, there is value in collecting and sharing the knowledge and experiences of the former government in implementing CL policy. This information could help other countries aiming to issue CL to avoid the unanticipated effects occurred in the Thai case.

In addition, actors who participated in the CL policy process played an important role in its success. Policy support included inter-ministerial committees, authorized central and local agencies, and also other stakeholders, especially NGOs and academics. The NGOs passionately protested against transnational drug industries, while academics provided concrete evidence to support the policy. The experiences of the former government highlighted that academics played a significant role throughout the CL policy process. Academics established the evidence base about problems related to patentability to encourage concerned sectors to develop a rigorous system of drug patentability as an alternative measure to avoid using CL policy. Academics conducted a study to estimate the potential implications of CL policy to help the government in making decisions based on

evidence. Academics also conducted clinical studies to assure the quality of CL generic drugs in order to boost practitioners' confidence in the quality of generic drugs procured under the policy. Finally, the policy performance and implications were evaluated by academics in order to inform stakeholders and educate the public.

The approach had several limitations. First, as the CL policy was introduced in Thailand eight years ago, although the policy is still active, it was impossible to directly observe the policy areas of agenda setting and policy formulation. Second, many interviewees were unable to recall all of the events that occurred in the past. This limitation leads to some difficulties in identifying policy elements in the process of policy-making and implementation. Third, the policy is politically sensitive. Crucially this suggests that some interviewees may tend to conceal particular issues, such as failure, mismanagement, or poor practices concerning the policy. Fourth, given the norms of Thai culture, subordinates might hesitate to criticise senior staff, or policy partners might be reluctant to criticise each other. To mitigate these limitations, sources of information were retrieved from several data sources and different groups of informants in order to verify findings as far as possible.

In addition, one of the key limitations of my study is the small number of interviewees. The framework developed in this study was based on information from policy makers, government officers and partners of the government including: NGOs and academics, who supported the policy; the generic drug industries, who provided the CL generic drugs; and the health care professionals, who used the CL drugs in hospitals. These groups of stakeholders were set as the priority group from whom the information was collected. Although I was unable to interview the patented drug industries, inter-governmental organizations, and other relevant ministries such as the Ministry of Foreign Affairs (MFA) and the Ministry of Commerce (MOC), due to the time limitation, I collected the views of these groups from literature.

As the CL policy was introduced in Thailand eight years ago, I found that some of the interviewees were unable to recall all of the events that occurred in the past. Therefore, I believed that the best reliable information for developing the framework were mainly obtained from literature, such as official letters, meeting

minutes, conference reports, which documented at the time of events. In my field work, I found abundant literature, which documented information from and opinions of various stakeholders including MoPH, MOC, MFA, NGOs, inter-governmental organization, and patented industries. These data sources sufficiently triangulated information among different groups of stakeholders.

In conclusion, although most of the important elements were already mentioned in Chapter 5, elements from experiences of the former government helped strengthen the framework with respect to the processes of decision-making and implementation of drug policy, focusing on CL policy.

Chapter 9: Discussion and conclusions of the thesis

9.1 Introduction

Patent protection for pharmaceutical products can create incentives for research and development of new medicines. However, it is acknowledged that the global patent regime does not necessarily address the needs of the developing world, instead creating barriers to access to essential drugs through pharmaceutical patent protection. Therefore, a series of remedial flexibilities have been included in the TRIPS agreement in order to allow countries to use the flexibilities of TRIPS to protect public health and promote access to essential medicines for their citizens. One of the flexibilities is the compulsory licensing (CL) policy; however, only few LMICs have made use of CL. Possible explanations for the low uptake of CL is that most countries are worried about the potential political and economic retaliations, and they are uncertain about which implementation strategies might help optimise benefits and avoid negative consequences. In the case of Thailand, the former government issued and implemented CL policy through learning by doing, and there were a number of unanticipated events. The knowledge acquired and lessons learnt from experiences of the former government are of value for developing a framework. Therefore, the framework developed under this study suggests key elements to be considered for decision-making and implementation of drug policy, focusing on CL policy.

The aim of this chapter is to provide a discussion and synthesis of all findings by clarifying roles of each policy element in the framework and the interactions between them. In addition, key findings for each policy process: agenda setting, policy formulation, implementation and monitoring are provided. Other issues around CL implementation, such as improving policy efficiency, and encouraging strategic roles of actors at each stage, are also addressed. Complementary information was included, such as other countries' experiences of the policy, in order to strengthen and validate the study findings. Finally, this chapter closes with policy recommendations for the Thai government about the current and future use of CL policy to improve its performance, and for other countries having the similar context to learn from the Thai experiences.

In this study, CL is suggested to be one of the policies to promote drug access in Thailand. The inclusion of CL as an institutional component in the Thai drug policy helps offer an additional measure beside the available measures, such as patent opposition and price negotiation, to policy makers. After the failure from these measures, the CL policy can be applied in case of public non-commercial use, in order to achieve the aims of the Thai universal coverage policy. In addition, the CL policy can be used to solve public health problems in the management of national emergencies. Therefore, the Thai government should keep the CL policy as an institutional element that can safeguard public health benefits of the country. This is completely compatible with TRIPs. The findings of this study could be beneficial, if the Thai government needs to use CL again in the future.

To develop the framework, my study contained four objectives as follows. In objective 1, an intensive review was conducted to identify policy elements affecting the decision-making and implementation of the policy from literature published by intergovernmental organisations. The contents of the preliminary framework were assessed by qualitative approaches in objective 4. Any additional elements derived from experiences and insights of CL implementation by the former government of Thailand were used to strengthen the framework. Moreover, there are implementation strategies identified in this study. In objective 2, potential implications across different drug types were analysed to identify key elements that should be incorporated in the drug selection criteria, and the performance of the Thai government in implementing the policy was evaluated in objective 3 to develop strategies to improve the government's performance. The findings of each objective are shown in figure 9.1.

According to the findings in objective 1 and 4, key elements were identified for inclusion in the framework. In the framework, policy elements include: policy contents in terms of activities and instruments required to implement the policy; contextual factors required to support policy implementation; actors required to participate in the policy process; and policy processes containing four stages: agenda setting, policy formulation, implementation, and monitoring. The details are as follows.

At the agenda setting stage, there are four main activities: (i) identification of unaffordable drugs, (ii) consideration for patent opposition, (iii) consideration for price negotiations, and (iv) consideration for using TRIPS flexibilities. In this stage, the combination of an unmet public health need and the availability of TRIPS flexibilities is an important contextual factor leading to the decision to put CL policy onto the national agenda. Experiences from the Thai government indicated that there are three additional contextual factors at this stage: (i) political standpoints of policy makers, (ii) strong networks of policy elites and partners, and (iii) political commitment to universal coverage. The key actors influentially participating in the process of agenda setting are multi-ministerial committees and patented drug industries; other additional actors include academics, NGOs, and patient groups.

In the stage of policy formulation, there are four main activities: (i) development of a CL policy proposal, (ii) identification of generic drug sources, (iii) development of streamlined procedures; and (iv) establishment of evidence base of CL to support the policy decision. The last activity is suggested by the experiences of the former government. The main contextual factor in this stage is the common misconception of TRIPs flexibilities. In addition, the experiences of the Thai government indicate three additional contextual factors influencing the policy formulation: (i) pressure from policy opponents, (ii) strong networks of policy elites and partners, and (iii) social values of policy supporters. The key actors in this stage are similar to the previous stage, but include two additional groups: (i) policy supporting groups, including international NGO and international academic groups; and (ii) policy opponent groups, including transnational-patented drug companies, and countries representing the patented drug firms.

There are six main activities for policy implementation and monitoring: (i) procurement of CL drugs, (ii) quality assurance of CL drugs, (iii) distribution of CL drugs to health facilities, (iv) utilization of CL drugs by health practitioners, (v) monitoring and evaluation of CL performance, and (iv) development of policy feedback. The key actors in this stage are authorised agencies responsible for the policy implementation, and academics are essential to adding in the framework. The main contextual factors to consider at this stage are institutional capacities (infrastructure and staff expertise) to implement the policy and to monitor and evaluate the policy performance. In addition, the experience of the former

government identified four additional contextual factors: (i) interruptions of drug supply from foreign suppliers, (ii) capacity of local generic drug industries, (iii) physicians' attitudes to the quality of generic drugs, and (iv) emerging need for knowledge of CL implementation.

Moreover, the findings in objective 2 suggest key factors, which should be included in the CL drug selection criteria. The key elements are: (i) drugs for treatment of diseases that are the leading causes of public health burden; (ii) drugs with the highest potential difference in treatment cost; and (iii) drugs that are required for diseases with no alternative treatments. The criteria could promote the transparency of policy decision process, and help policy makers to select the drugs, which potentially create the highest benefits to the society.

Furthermore, findings in objective 3 suggest implementation areas, which merit more government attention in order to improve performance. The implementation areas are prioritised as follows: (i) most vitally, improving physicians' attitudes to the quality of CL drugs; (ii) managing the risk of interruptions of drug supply from foreign suppliers, which significantly affected the implications of CL policy; (iii) strengthening the capacities of local drug industries to maintain drug supply in the long run; and (iv) Encouraging feedback from local facilities in order to improve CL performance and implications.

<p>- Objective 1: To develop a preliminary analytical framework for CL decision making and implementation.</p> <p>- Objective 4: To assess applicability of the analytical framework from objective 1 with CL cases in Thailand.</p> <p>Policy elements were identified from literature of intergovernmental sectors, and strengthen by the Thai CLs.</p>					<p>- Objective 2: To estimate lifetime treatment cost saving due to CL implementation</p>
<p>Process Contexts Contents Activities, and Instruments Actors</p>					<p>Criteria for CL drug selection</p>
<p>Agenda setting</p>	<p>C1.1: Unmet public health need and TRIPS</p>	<p>A1.1: Identification of unaffordable drugs, and need assessment system, drug selection criteria</p>	<p>P1 Government Multi-ministerial committees</p> <p>Non-Government Patented firms <i>Academics, NGOs, Patient groups</i></p>	<p>To achieve the maximum benefits from the use of CL policy, the criteria of drug selection should incorporate the following elements:</p>	
	<p><i>C1.2: Political standpoints of policy makers</i></p>	<p>A1.2: Consideration for patent opposition, and patentability database, guidelines</p>			
	<p><i>C1.3: Strong networks of policy elites and partners</i></p>	<p>A1.3: Consideration for price negotiations, and drug price data, negotiation guidelines</p>			
	<p><i>C1.4: Political commitment for the universal coverage</i></p>	<p>A1.4: Consideration for using TRIPS flexibilities, and drug information system, policy guidelines</p>			
<p>Policy formulation</p>	<p>C2.1: Common misconception of TRIPS flexibilities</p>	<p>A2.1: Development of CL policy proposal, and national patent law incorporating with TRIPS</p>	<p>P2 Government multi-ministerial committees</p> <p>Non-Government Generic firms <i>Academics, NGOs</i></p> <p>International <i>Inter-NGOs, Inter-academics, Transnational firms</i></p>	<p>(1) Diseases as the leading causes of public health burden;</p> <p>(2) Drugs with the highest difference in treatment cost compared to current practices;</p> <p>(3) Drugs which are required to use for diseases having no alternative treatments.</p>	
	<p><i>C2.2: Pressure from policy opponents</i></p>	<p>A2.2: Identification of generic drug sources, and the list of prequalified generic medicines</p>			
	<p><i>C2.3: Strong networks of policy elites and partners</i></p>	<p>A2.3: Development of streamlined procedure, and the list of prequalified quality control laboratories</p>			
	<p><i>C2.4: Social values of policy supporters</i></p>	<p><i>A2.4: Establishment of evidence base of CL policy, and communication channel to stakeholders</i></p>			
<p>Process Contexts Contents Activities and Instruments Actors</p>					<p>- Objective 3: To evaluate the CL policy performance</p>
<p>Policy implementation</p>	<p>C3.1: Capacities of agencies implementing the policy</p>	<p>A3.1: production or procurements of generic drug products, and guidelines for drug procurement</p>	<p>P3 Government Health Ministry, Drug regulatory agencies, Health benefit schemes, Health specialists related patients</p> <p>Non-Government Generic firms, <i>Academics,</i></p> <p>International International concerned agencies</p>	<p>Prioritized elements for performance improvement</p> <p>To achieve the maximum benefits, four elements should be prioritised for improving policy performance as follows.</p>	
	<p><i>C3.2: Interruptions of drug supply from foreign suppliers</i></p>	<p>A3.2: Quality assurance of generic products, and guidelines for quality assurance</p>			
	<p><i>C3.3: Capacities of local generic drug industries</i></p>	<p>A3.3: Drug distribution to health facilities, and guidelines for drug distribution, <i>VMI</i></p>			
	<p><i>C3.4: Physicians' perceptions of the quality of generic drug</i></p>	<p>A3.4: Drug utilization at health practitioners, and clinical practice guidelines, <i>RDU</i></p>			
<p>Policy monitoring</p>	<p>C4.1: Institutional capacities for monitoring & evaluation</p>	<p>A4.1: Monitoring and evaluation of CL policy, and information system for policy monitoring</p>	<p>P4 Government Monitoring agencies of CL policy</p> <p>Non-Government <i>Academics,</i></p>	<p>(1) The physicians' attitudes on quality of CL drugs.</p> <p>(2) The unanticipated effects from foreign suppliers.</p> <p>(3) The capacities of local drug industries to maintain drug supply in the long run.</p> <p>(4) Policy feedbacks from local health care facilities for improving CL implications.</p>	
	<p><i>C4.2: Emerging needs for knowledge about policy experiences and implications</i></p>	<p>A4.2: Development of policy feedback, and channel to deliver policy feedback</p>			
<p>Additional elements from objective 4 analysis are in <i>italic and underlined letters</i></p>					

Figure 9. 1 Summary of findings from this study

The PhD findings contain strategies to optimise the positive consequences and minimise the negative consequences. According to the systematic review in chapter 2, there are three positive consequences: (i) increase in public health benefits, (ii) increase in consumer welfare, and (iii) decrease in market prices of pharmaceutical products. My findings suggest that the positive consequences can be optimised by improving the performance in implementing the policy. The government should improve its performance through three contextual elements: preparing a supportive system to prevent interruptions of foreign drug supply, strengthening capacity of local generic drug industries, and strengthening physicians' confidence on the quality of generic drugs. Moreover, the findings suggest key indicators that should be incorporated in the criteria of drug selection, in order to achieve the highest benefits of the policy on certain drugs. These suggestions could help the Thai government optimize the positive consequences of CL policy.

In addition, three negative consequences were found in the literature review: (i) disincentive for drug innovations, (ii) delay of new drug launches, and (iii) deterioration of the national economy. Strategies to lessen or mitigate the negative consequences were identified. As most negative consequences result from pressure of policy opponents, my study suggested three approaches to prevent the negative reactions of stakeholders. First, the government should clearly declare the aim and scope of CL implementation to avoid misinterpretation among stakeholders. Secondly, the use of CL policy under the ideological aim of universal access to essential drugs could be an appropriate ground for the CL justification. Thirdly, if any negative reactions from policy opponents still occur, strong networks of policy elites and partners could create a third force to support the use of CL and resist the opponents' pressure. Furthermore, my findings suggest to avoid the potential negative consequences of CL that Thai government should also consider other alternatives, including patent opposition, price regulation and negotiation, parallel import, and voluntary licensing, in order to avoid using CL policy and subsequently avoid the potential negative consequences of CL.

9.2 Key findings in the stage of agenda setting

9.2.1 Essential elements leading to a decision to issue CL policy

According to the study findings, an unmet public health need caused by unaffordable patented medicines prompted policymakers and elites to find a policy solution. The former Thai government was faced with budget burdens in health care treatment for three life-threatening diseases: HIV/AIDS, cerebrovascular disease, and cancer, and these burdens led to the CL decisions [81] [83]. However, the government had never used this policy before, despite having the problem for a long time. It is clear that, beside the unmet public health needs, there must be other essential elements leading to the decision to issue CL. Examining the experiences of the former government highlights that three additional contextual elements influence the setting of CL policy.

- **Political standpoints of policy makers on health over trade interests:** Among several alternative measures to promote drug access, CL policy highlights conflicts between trade and health interests. As most countries issuing CL policy were confronted with strong negative reactions from patent owners, many LMICs have been reluctant to grant the policy [19, 20]. However, Thailand is a leader in many aspects of public health policy, including the areas of drug access, and the leadership of policy makers and politicians is a key factor leading to the decision to implement CL despite conflicts with other stakeholders [20, 229]. This point is consistent with CL in Ecuador. For example, the Ecuadorian President expressed his political viewpoint that “This is our vision of intellectual property. It's not a mechanism to enrich the pharmaceutical or agrochemical companies. It's a mechanism for development for the people” [64]. Consequently, in Ecuador CL was chosen and pursued to achieve drug access.

- **Strong networks of policy elites and partners:** A policy analysis study refers to the model of "the triangle that moves the mountain" to explain key factors influencing successful decisions when issuing CL policy [20]. It highlights that, in addition to the political standpoint of policy makers mentioned earlier, other two angles in the model were (i) the knowledge generated by academic groups and (ii) the movement of civil society [20, 229]. The findings in Chapter 8 highlight that strong institutional networks and stakeholder participation (especially health

professionals, academics, health NGO networks and patient groups) played an important role in successfully developing the policy and placing the problem of drug access and CL policy on the national agenda. In addition, the former government established an inter-ministerial committee, consisting of public health, trade, industry and foreign affairs, to participate in policy decision-making process. This point is supported by the fact that ministerial collaboration is often necessary to develop a partnership between ministries, and also to promote policy coherence across issues concerning the interaction of trade and health. [245].

- **Political commitment to achieving universal health care coverage:** According to the findings in Chapter 8, the former government argued that the decision of CL policy was made to support the universal health care coverage by improving access to essential medicines for all patients in need [81, 83]. The universal access program has also been implemented in Brazil and CL policy is one of the essential measures used to sustain universal access to ARV drugs [246]. The ideological aims of universal access to medicines, as the duty of the government to promote the right of its citizens in access to essential drugs, can help to justify the use of CL policy to serve public health interests. Therefore, any license used to support the national public health program could be an appropriate ground for the CL justification. It is consistently mentioned by Pogge *et al.* that the national program of universal access to essential medicines may become an important context, which justifies issuing CL policy [247].

9.2.2 Criteria for selecting drugs to issue CL policy

According to the literature review in Chapter 2, an interesting case of CL in LMICs is Egypt, which used CL on Viagra[®]. Stakeholders raised doubts about whether increasing access to the drug was essential to public health interest [33]. This suggests that a transparent process is required when selecting drugs to be issued under CL policy, a point consistently mentioned in Chapter 5 and 8.

Clear criteria for selecting drugs to serve unmet public health needs could help promote the transparency and effectiveness of the CL decision on a particular drug. A previous study provided explicit drug selection criteria for CL policy as follows: (i) the number of patients in need of the drugs, which could be estimated by

using epidemiological data of disease prevalence and incidence; (ii) the difference in prices between currently available patented drugs and the proposed generic drugs; (iii) the safety and efficacy of the drugs of interest by comparing with alternatives currently available on the market; (iv) the remaining duration of term of patent protection of the original drug in question; (v) variations in prescription practices of health professionals and the potential for irrational use of particular drugs; and (vi) the preparedness of streamlined procedures for registration, importation and distribution of generic drugs under CL policy [70].

The findings from my study are consistent with the previous suggestions, but add some important factors to the first three points. The findings in Chapter 6 suggest that the drug selection criteria should be adjusted as follows: (i) it should target not only diseases affecting a high number of patients, but also diseases causing a high burden to the country. The leading causes of public health burden (such as diseases listed in the national burden of disease, which takes mortality and morbidity into account), should be employed; (ii) it should not only look at the difference in prices between patented and generic drugs, but rather analyse the difference in total treatment cost, between potential CL drugs and current practices; (iii) it should not only select the drug with the highest safety and efficacy records, but also drugs required to use for diseases with “no alternative treatments”. The revisions of drug selection criteria suggested above could help policy makers and elites to cautiously consider the drugs, which potentially create the highest benefits to the society.

9.2.3 Alternatives to CL policy

It has been argued that the decision to apply CL should be made only when necessary, after failures in properly trying other alternatives [148]. However, there are two areas, in which the government needs to improve its performance when engaging in alternatives to CL. First, the government should develop the quality and usability of the patent information system. The key problem for Thai implementation of CL is the lack of a high-quality domestic information system for pharmaceutical patents. As mentioned in Chapter 8, the government issued an unnecessary CL for letrozole because no effective and comprehensive database

system is available for the patent investigation. The patent database in Thailand is unstable, very complex and time-consuming to use, effecting the certainty for making a decision. Concerns over the pharmaceutical patent database are supported by Yamabhai *et al.*, who argue that the drug patent information system in Thailand should be strengthened to be more effectively used for public health interests [219].

Second, the government should develop effective mechanisms to control or manage the price of drugs. Regarding the issue of drug price, price negotiations of the former government with patent owners failed to obtain price reductions for most of the drugs in question. Imatinib is the only successful case: the patent owner, Novartis, agreed to provide imatinib for all patients under the Glivec[®] International Patient Assistance Program (GIPAP). As such, price negotiation enabled the government to avoid using CL for Imatinib. In addition, evidence suggests that CL seems to be an effective threat in price negotiations to patent firms. For example, the Brazilian government successfully used the threat of issuing CL policy to obtain significant price reductions from the patent industries [73]. Another point of concern is that Thailand seems to have ineffective measures to control medicine prices, leading to high drug prices which are sometimes unaffordable for the government and patients [90]. Therefore, to overcome the problem in long-term, the Thai government should develop rigorous national legislation to control the price of essential drugs, especially the patented pharmaceutical products.

9.3 Key findings for the policy formulation stage

9.3.1 Common misconceptions of CL provisions

Misconceptions of CL policy provision is the main contextual element identified in Chapter 5. For example, according to the TRIPS article 31, the use of CL is not restricted to situations of national emergency and in the case of other circumstances of extreme urgency, but rather “in cases of public non-commercial use”. In addition, the public health crises, including “but not restricted to” those concerning HIV/AIDS, tuberculosis, malaria, and other epidemics, can represent a national emergency or other circumstances of extreme urgency [24]. The findings in Chapter 8 highlighted that, although the Thai government issued the CL policy for

public non-commercial use (compliant with the TRIPS agreement), the government was still faced with negative reactions from policy opponents [234]. Therefore, the availability of the TRIPS agreement may be not sufficient, but the correct conception and consistent interpretation of stakeholders is also essential in order to avoid improper interruption of CL implementation.

The findings from Chapter 8 also addressed effective strategies used by the Thai government to adjust stakeholder misconceptions of the Thai CLs. The government published two official white papers in order to clarify facts and evidence on the key issues related to the government use of patents on ARV, cardiovascular and cancer drugs. The Thai government clarified in its white paper that the rationale behind the use of CL policy complied with the provision of TRIPS [81, 83]. In addition, a series of activities was conducted by the former government and its partners, such as: publishing formal and informal documents and disseminating them to the public, making speeches at national and international meetings, visiting foreign countries that criticized Thailand, and inviting inter-governmental organizations to investigate the implementation of CL policy in Thailand. These strategies succeeded in adjusting the misconceptions of concerned stakeholders, and developing policy support from sectors outside public health [88]. These effective strategies should be recorded as key policy elements for any future CL use in Thailand and other countries.

9.3.2 Common threats to be aware of when issuing CL policy

Policy opponents commonly put political and economic pressures on the countries issuing CL policy. The results from the systematic review of CL implications in Chapter 2 and the findings from the Thai experiences in Chapter 8 consistently indicated that transnational patented drug companies and countries representing such companies commonly try to put pressure on countries issuing the CL. An effective strategy to deal with the threats and negative reactions is a strong network of policy partners. The findings from Chapter 8 indicated that negative reactions from policy opponents were mitigated through support from the policy networks. The concerned supporters were local organisations, such as local NGOs, patient groups and academics as well as international organisations. This is consistent with the CL case in Brazil, where the Brazilian government gained

support for its decision from several sectors [248]. Collaboration between policy supporters played an important role in the success of CL implementation: while NGOs strongly protested against transnational drug industries, academics provided evidence to support the policy [20, 229]. Therefore, teamwork between government and non-government organisations could create a third force to enhance CL-implementing countries' power to resist such pressure.

9.4 Key findings for the policy implementation stage

9.4.1 The quality of generic drugs under CL policy

One key element influencing the success or failure of CL implementation is practitioner confidence in the quality of generic substitutes. A number of studies have criticised the quality of generic drugs from India and China, both major international suppliers of generic drugs. For example, Feldman argued that concerns about low-quality drugs arose from the fact that quality-control inspections are rarely conducted by the Food and Drug Administrations in India or China, meaning these generic drugs are potentially unsafe and/or ineffective [249]. Uncertainty about the quality of generic drugs makes physicians hesitant to prescribe the generic CL drugs, and this may produce significant problems in the public health system. Evidence from findings in Chapter 7 indicated that the lack of confidence in the quality of CL generic drugs to substitute its patented version among Thai prescribers created the highest monetary loss (approximately 119 million US\$ during 2012 to 2014) in Thailand. The confidence of practitioners in the quality of generic substitution affects the practitioners' acceptance of, and dedication to activities undertaken under the policy [250]. Such significant costs suggest that resolving the issue should be a priority for the government.

Based on findings from Chapters 5 and 8, several strategies might build confidence in the quality of CL generic drugs. For example, the drugs could be selected from the WHO list of prequalified medicinal products; any drug not obtained from the list could be quality assured by a laboratory, itself prequalified by the WHO. This practice is consistent with CL in Brazil, which implemented CL policy by using generic versions prequalified by the WHO [246]. However, because even the best quality assurance systems may not prevent occasional production

failures, the drug production process must adhere to the Good Manufacturing Practices (GMP) standard and comply with requirements for quality specifications. In addition, random representative sampling and testing should be done to verify compliance with standards and references given. Another issue is the lack of regulation in drug promotion and advertisement, which can also cause serious problems for CL implementation. It has been reported that aggressive and misleading advertising of brands has influenced patients against generic drugs [157]. Advertising regulation is essential to avoid the misleading advertisements for drugs. The series of mechanisms mentioned above should build up confidence and create positive perceptions of the quality of CL generic drugs.

9.4.2 Interruptions in drug supply under CL policy

Another key issue in the implementation stage is interruptions in drug supply. The Chapter 7 performance evaluation for drug procurement showed that clopidogrel, letrozole and docetaxel were directly imported from a limited number of foreign generic manufacturers. The government was faced with a problem of supply interruptions of the drugs several times, which itself has serious consequences. For example, the interruptions in supply of the three CL drugs created monetary loss (approximately 5.9 million US\$ during 2010 to 2014). The Thai government took a high risk when the foreign generic suppliers did not deliver the drugs on time or the quality of supplied drugs failed to meet an acceptable national standard. In addition, interruptions in supply mean danger to patients because of the risk of treatment failure, and the possibility of developing drug resistance leading to lost health, social, and economic benefits to the country. This seems to be a strong argument for increased government focus on securing a range of drug suppliers. The argument is also supported by the case of efavirenz. As efavirenz has five generic drug suppliers cooperating with the GPO to supply the product under CL policy, there are no unanticipated effects from an interruption in supply during the CL period. Therefore, this is a key issue that authorised agencies should be concerned about when the CL drugs are mainly procured from foreign suppliers. This is supported by Bate *et al.*, who argue that there are difficulties in controlling or predicting the external factors of foreign generic manufacturers for delivering qualified generic drugs to meet local context-specific demands [251].

In addition to the reliance on foreign drug industries, domestic industries should be strengthened in order to play an important role in maintaining a continuous CL drug supply. Through knowledge and technology transfer, CL policy can play a crucial role in developing and fostering local generic drug industries [252]. The findings from Chapter 7 supported this point. LPV/r has been locally produced by the GPO itself through technology transfer and never faced with any interruption in supply because the drug has been managed as a national priority. The GPO took complete responsibility for meeting the national demand for LPV/r, (this commitment also brought the price of Indian generic suppliers down in an attempt to compete). It can be seen that the capacity of local drug industries is another element contributing to ensuring steady long-term drug supply. This statement is supported by WHO, which comments that local drug industries should be strengthened to continuously maintain national drug supply, and establishing a network of drug suppliers for the country is also essential [253]. The strong network could overcome the unanticipated effects posed by foreign generic drug suppliers in terms of interruptions or long lead times in drug supply.

There is, however, an important precaution concerning the price of drugs produced by local industries. Where medicines are produced locally there tends to be an expectation that their prices will be more in line with the purchasing parity of the local population; however, this may not always be the case. For example, it was shown in Chapter 7 that the GPO aimed to produce efavirenz locally, through technology transfer, but the decision was reversed because purchasing generic efavirenz from India was cheaper than local production. It can be seen that locally produced generic medicines may not be cheaper than their imported equivalents, unless a combination of efficiencies in production and economies of scale can be achieved [253]. Therefore, policy makers should be wary of assuming that local drug production is always the cheapest or most efficient mechanism.

9.5 Key findings in the stage of policy monitoring

9.5.1 Supportive system for monitoring CL performance

According to the TRIPS agreement and Thai patent law, the legal validity of any CL decision can be subject to judicial review by authorised agencies. Therefore,

at the policy monitoring stage, the policy implementation is monitored and evaluated by authorised agencies to analyse whether the performance meets expectations and complies with the policy proposal. In response to the policy review, the former government used two instruments to support the process. First, the Vendor Managed Inventory (VMI) system to control the distribution of CL drugs was used to monitor whether the drugs were distributed only to patients eligible under the CL protocol. Second, the Rational Drug Use (RDU) system was used to monitor whether CL drugs were utilised in compliance with the defined treatment indications within the scope of the policy proposal.

9.5.2 Channels to communicate with stakeholders and public

Problems, obstacles, and defects arising from the policy were identified to develop policy feedback to improve efficiency and effectiveness. The information is beneficial not only to policy makers and authorised agencies, but also helps other stakeholders to understand the situation. The former government used two main approaches: vertical and horizontal communication. First, the experiences of the former government indicate that a purely top-down policy is not sufficient. When the policy was transformed into work plans, feedback from local staff is essential because there was a need to engage with local staff to achieve their acceptance of, trust in, and compliance with the policy. Therefore, the government should allow operating units in health care facilities to feed back their experiences through bottom-up suggestions. This argument is consistently mentioned in Chapter 7 and 8. Second, horizontal communication is required to communicate with stakeholders and the public. Mass media can be used to attract politician and public interest, and to harness reactions from other stakeholders. Evidence suggests that an NGO-supported mass media campaign successfully pressured a patented drug firm to change their behaviour in order to maintain their positive social image [254]. In addition, Chapter 8 found that the former government also effectively used international meetings and conferences to disseminate information to the public and exchange experiences with other countries.

9.6 Strategies to improve efficiency of the CL process

In this study, the policy processes were simplified by using heuristic stages, which assume a linearity to the public policy process: agenda setting, formulation, implementation and monitoring. However, policy analysts have argued that the idea of a linear process may not reflect reality [136]. The findings from the CL cases of Thailand support this argument: the former policy makers worked on different policy processes simultaneously, in order to improve policy efficiency.

The simultaneous approach was employed in the process of decision-making and implementation. According to the findings from Chapter 8, patent owners tended to extend the negotiation period in order to delay the implementation of CL policy. As a result, the government negotiated with patented drug firms alongside the formulation of CL policy. In addition, the legal validity of any CL decision is subject to judicial review by courts or other authorised agencies as mentioned earlier. The use of CL may be delayed if the patent owners appeal the validity of the license used or the kind and level of remuneration granted under the policy. Therefore, the parallel work also occurred in the process of policy implementation and monitoring. This point is consistent with the Indian case, in which applications for CL policy could be delayed by CL oppositions, thus limiting the effectiveness of this policy [255]. It is, therefore, suggested that, once the decision is made, the government should fully implement the policy even while appeal procedures are being operated by other parties, as these approaches can avoid the delay in implementing the policy.

9.7 Strategic roles of actors in each stage of policy process

Multi ministries and multi-disciplinary stakeholders are essential. This statement is consistent in the case of Thailand and India. Key actors include Ministry of Public Health, Industry, Commerce, Foreign Affairs, and other authorised agencies in central sectors and local health care facilities, played a significant role in the policy processes [221, 256]. In addition, other stakeholders such as the NGOs and academics are regularly invited, in order to enhance policy partnership [221, 256]. Especially, academic groups play a significant role in the CL policy process. According to experiences of the former government, the finding in

Chapter 8 indicated that *in agenda setting*, academics established empirical evidence to encourage the government to develop a rigorous system of patentability for pharmaceuticals. *In the formulation stage*, academics and NGO groups played a significant and positive role in supporting CL policy against the policy opponents. *In the implementation stage*, academics conducted clinical studies to confirm the equivalent quality of CL generic drugs compared to its patented version to boost practitioner confidence in CL drug quality. *In the policy monitoring stage*, empirical studies from Thai academics were presented in many important meetings and to a wide range of stakeholders, in order not only to communicate with stakeholders, but also to educate other ministries and foreign countries. It can be seen that there are several actors in the CL policy processes, with academics playing a key role. This is consistent with Almeida *et al.* addressed that research results are seen as having a significant impact on the public policy process. Integration between researchers and decision makers seems to condition the ways in which research results are used in policies [257].

9.8 Policy recommendations

For the Thai government for the current use of CL policy

Based on the evaluation of the Thai government's performance in implementing CL policy, there are several suggestions for ways in which the Thai government could improve its performance. (1) Improving physicians' confidence on the quality of CL drugs is the priority as it created the highest costs in CL implementation. (2) The issue of supply interruption effects from foreign suppliers, which sometimes provide generic drugs of unacceptable quality or late delivery, significantly affected the implementation of CL policy; and the capacities of local drug industries should be strengthened to maintain a consistent long-term drug supply. (3) The implementation step required performance monitoring and feedback from local operating units such as health care facilities to improve CL policy implementation performance.

1. To boost physician confidence in the quality of CL drugs, several strategies should be applied, such as: selecting drugs from the WHO list of prequalified medicine products; drugs not obtained from that list should be quality-assured by a laboratory prequalified by the WHO. Testing should be done periodically to verify compliance with standards and references given, and evidence of quality assurance should be accessible to drug prescribers. In addition, advertising regulation should be strengthened to avoid misleading advertisement, which encourages people to become averse to generics.

2. To mitigate the risk of supply interruptions effects from foreign suppliers, procurement agencies should consider the number of qualified suppliers available in the market. Where there is a limited number of drug suppliers, local production through technology transfer should also be managed as a priority. Therefore, local capacity in terms of infrastructure and personal expertise has to be strengthened in order to choose and replicate new transferred technologies wisely. The government should establish local research and manufacturing capacity to meet public health needs and ensure sustainability of the long-term drug supply system.

3. To improve policy implementation, it is essential that central agencies and peripheral health facilities collaborate in the monitoring of policy performance.

Effective communication approaches through regular meetings among policy networks and public hearing approaches to obtain feedback of stakeholders should be maintained, as it plays a crucial role in identifying the problems and solutions to improve the CL policy performance.

For the Thai government for future use of CL policy

1. To achieve maximum benefits, the key parameters that should be incorporated in the drug selection criteria are: (i) Drugs for treatment of diseases which are the leading causes of the public health burden, (ii) Drugs which offer the highest difference in treatment cost saving compared to current practices, (iii) Drugs which are required for diseases with no alternative treatments, and (iv) The remaining duration of patent protection for the relevant drug. These criteria should be applied in order to determine which drugs to select if CL is required in the future.

2. There are alternative measures to be considered prior to the use of CL such as patent oppositions and price negotiations. However, the Thai government should pay more attention to: (i) strengthening the use of rigorous criteria for patentability and implementing guidelines for patent examination; (ii) strengthening the patent information system so it can be effectively used for public health interests; (iii) strengthening national legislation to control the price of essential drugs under patent protection. CL policy may be applied when necessary after failures in trying other alternative measures. In addition, the Thai government has never used parallel imports. Therefore, the government should design a comprehensive procedure and assign a responsible agency to perform the parallel import policy.

3. The issues to be considered in formulating a proposal to issue CL policy include: (i) scope of product which should include all subject elements covered by the patent in question, (ii) duration which should last until the patent expiration or there is no more essential need for the drug, (iii) remuneration rate which should comply with international standard guidelines, and (iv) target population of drug users which should not be limited to patients entitled under the three schemes (UC, SSS and CSMBS), since this may deprive some patient groups, especially stateless people, an ignored group of patients by the current CL policy in Thailand.

4. Any decision concerning the grant of CL policy can be subject to judicial review by courts or other authorised agencies, key supportive instruments, including Vendor Managed Inventory (VMI) and Rational Drug Use (RDU), to monitor the performance of CL policy implementation should be maintained if CL is required in the future. (i) The VMI system can be used to check that the drugs are distributed only to patients under the scope of CL protocol and are not leaked to other users (such as private sectors), which would contradict the declared notifications. (ii) The RDU system can be used to monitor the utilisation of CL drugs. As the prices of CL drugs are substantially lower than the drugs used prior to the granting of the policy; this may lead to overutilization of drugs. Protocol guidelines of CL drug utilisation and clinical practice should be established to promote the rational use of the drugs. The information on both systems is essential for any judicial review.

5. It was highlighted that there were misunderstandings between central agencies and local health facilities because there are no coordinators to provide essential information. Therefore, the Thai government should establish a coordination and consultation unit equipped with experts to answer questions about the policy promptly. This unit should deal with both policy partners and the public in order to create trust and confidence in the MOPH's operation and lessen problems relating the policy implementation.

For other countries with similar contexts

1. Other countries could learn from the Thai CL experience. The Thai experience highlighted that, in addition to the problems of unmet needs in the public health system, there were three additional contextual elements, which influenced the agenda: (i) Political standpoints of policy makers on health over trade interests, (ii) Strong networks of policymakers and partners, and (iii) Political commitment to achieving universal health care coverage (one ground for CL justification).

2. Any government aiming to use CL policy should be aware of negative consequences in terms of political and economic retaliation from policy opponents. According to the Thai CL experience, key strategies, which should be considered prior to implementation of CL policy, are as follows. (i) The grounds for CL implementation for a particular drug should be clearly justified on case by case basis, in order to avoid negative reactions from stakeholders based on

misconceptions. (ii) If opponent reactions result from a certain interest of stakeholders against the use of a particular patent, strong networks of policy partners and social value of policy supporters could create a third force to enhance power for CL countries to resist such pressure.

3. A strength of CL implementation in Thailand is the participation of a range of stakeholders throughout the policy process. It is suggested that an inter-ministerial committee should be established at the agenda setting and policy formulation stages, in order to allow decision makers from concerned ministries, such as trade, industry and foreign affairs, to engage from the beginning of policy process. In addition, other stakeholders, such as NGOs and academics, should also be invited to participate. Both groups play an important role in CL policy process.

4. Finally, lessons learnt from Thailand indicated that countries aiming to use CL should conduct price negotiations in parallel with CL formulation in order to improve the efficiency of the policy process. In addition, parallel work may be conducted between policy implementation and monitoring, in order to prevent specious delays from appearing the patent validation to CL implementation. This approach was used effectively by the former Thai government and may be applied to other countries.

For further studies

1. This study focused mainly on insights derived from the Thai government experiences to develop the framework to aid decision-making and implementation of drug policy, focusing on CL policy. Since activities related to the policy processes were mainly carried out by the Ministry of Public Health (MoPH), the main weakness of this study is that the picture of policy process in non-MoPH and the private sectors may not be focused. To extend knowledge, there is value in analysing the views of other sectors, such as the government sectors in trade, industry, and foreign affairs; non-governmental organisation sectors from civil society and not-for-profit groups, as well as for-profit groups, such as patented and generic drug firms. The knowledge gained from the views of other concerned sectors may complement the findings of this study.

2. As only the case of Thailand was studied, the findings may not represent other LMIC contexts. However, some of the findings may be useful to apply in other countries where most elements of the health system are similar to the Thai context. Even in places with a different environment, this thesis may usefully contribute some aspects of lessons learnt on CL policy process, especially in resource-limited settings. However, further studies should be conducted in other contexts, and the findings should be compared with the Thai cases. Sharing experiences across different countries with different contexts are essential to complement and strengthen information and to gain more knowledge about the generalizability of the framework of CL policy.

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Appendices

Appendix 1: Ethical approval

London School of Hygiene & Tropical Medicine
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Observational / Interventions Research Ethics Committee

Mr Adun Mohara
Research Degree Student
PHP
LSHTM

9 September 2014

Dear Mr. Mohara,

Study Title: Compulsory licensing of pharmaceuticals in Thailand: Development of a framework for decision making and implementation of compulsory licensing

LSHTM Ethics Ref: 7765

Thank you for your letter of 8 September 2014, responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Information Sheet	Information sheet.docx	29/06/2014	1
Protocol / Proposal	CL in Thailand_Ethical approval_29_June 2014_EC.docx	29/06/2014	1
Information Sheet	Consent form_revised version.docx	23/08/2014	1

After ethical review

Any subsequent changes to the application must be submitted to the Committee via an Amendment form on the ethics online applications website. The Principal Investigator is reminded that all studies are also required to notify the ethics committee of any serious adverse events which occur during the project via an Adverse Event form on the ethics online applications website. At the end of the study, please notify the committee via an End of Study form on the ethics online applications website. Ethics online applications website link: <http://eo.lshtm.ac.uk>

Yours sincerely,



Professor John DH Porter
Chair

ethics@lshtm.ac.uk
<http://www.lshtm.ac.uk/ethics/>

Improving health worldwide

Appendix 2: Information sheet

Research title: Compulsory licensing of pharmaceuticals in Thailand: Development of a framework for decision making and implementation of compulsory licensing

This research is being led by the Health Intervention and Technology Assessment Programme (HITAP) in Thailand and the London School of Hygiene and Tropical Medicine (LSHTM).

Study objectives

Thailand has implemented Compulsory Licensing (CL) since 2006 to increase access to seven essential drugs for treatment of HIV/AIDS, cardiovascular disease and cancer. This study aims to develop a framework for decision making and implementation of CL policy. The framework will be applied for further decision to issue CL in Thailand, and may be applicable to other countries.

The project is funded by the Health Insurance System Research Office (HISRO) and takes place during August 2014 - December 2015.

Methods

The methods used will be interviews with key informants from the Thai government, academia, non-profit organizations, and the private sector.

Participation

I request your participation in this interview because I believe you may be able to contribute to my understanding about past experiences, the current situation and future requirements of CL policy in Thailand.

Taking part in the study is entirely voluntary and withdrawal is possible at any time without any penalty to you and without having to give a reason.

If you agree to take part in this research I would like to ask you some questions for between 30 - 60 minutes.

The research will in no way inconvenience you apart from the time it will take you to participate in this interview.

Confidentiality

The information that I gather from you and others will assist me in understanding the history and challenges of CL policy decision and implementation in Thailand. I will write reports and other outputs based on this information. I will maintain strict confidentiality throughout this study. Your name will not be linked to any quotes or other results of this study or included in any reports, even anonymously.

Your interview will be recorded with your permission. A researcher will be taking notes, which will be stored in secured rooms and computer files with access codes and will only be shared among study team members.

I appreciate your participation in this study. Thank you for your time and your effort. Again, if you have any questions or concerns about the study, please do not hesitate to contact the investigator at the detail below.

Mr. Adun Mohara

Health Intervention and Technology Assessment Programme (HITAP)

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The Institute for Development of Human Research Protection (IHRP) ethics panel approved this study on:

The London School of Hygiene and Tropical Medicine Ethical Committee approved this study on:

Appendix 3: Research participant consent form

Research Title: Compulsory licensing of pharmaceuticals in Thailand: Development of a framework for decision making and implementation of compulsory licensing

Contact information of local research institute: *Health Intervention and Technology Assessment Programme (HITAP), Ministry of Public Health, Tiwanon Road Nonthaburi 11000.*

**Please
initial box**

1. I confirm that I have read and understand the participant information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered fully.
2. I give consent for my quotes to be used in the research.
3. I understand that data collected during the study will be analysed by responsible individuals from the Health Intervention and Technology Assessment Programme (HITAP) and the London School of Hygiene & Tropical Medicine (LSHTM).
4. I agree to take part in the above study.

_____ Name of Participant (printed)	_____ Signature	_____ Date
_____ Name of Person taking consent	_____ Signature	_____ Date

1 copy for participant; 1 copy for study researcher

Appendix 4: Interview schedule

As there are very few actors in the area of CL policy in Thailand, their affiliations can be linked to the informants. Therefore, only codes and interview dates were provided in the interview schedule.

No.[Code]	Interview date
1.[GS01]	11 September 2014
2.[GS02]	13 October 2014
3.[AS01]	17 October 2014
4.[PS01]	17 October 2014
5.[NS01]	29 October 2014
6.[AS02]	5 November 2014
7.[GS03]	6 November 2014
8.[NS02]	12 November 2014
9. [GS04]	26 November 2014
10.[GS05]	3 December 2014
11.[HS01]	8 December 2014
12.[HS02]	17 December 2014
13.[HS03]	19 December 2014
14.[GS02]	11 February 2015 (Follow-up interview)
15.[GS03]	26 February 2015 (Follow-up interview)

Appendix 5: Data collection tools

There are two data collection tools. First, the list of semi-structured interview topic questions includes introductory and specific questions as follows: the questions about background information of informants, and their knowledge or opinion about policy activities, supportive instruments, contextual factors, and actors that influenced the Thai CL policy process. The policy process is classified into four stages: agenda setting, policy formulation, implementation, and monitoring. These questions were used to ask for all groups of informants.

1) Introductory questions:

1. What was your position at the time of decision-making and implementation of CL policy?
2. What were the responsibilities in your job relevant to decision-making and implementation of CL policy?

2) Specific questions:

1. From your view, what were the policy elements essential in the stage of agenda setting, and why they were essential:
 - 1.1 Contextual elements required to support the agenda setting for improving drug access.
 - 1.2 Activities required to set a national policy agenda to improve drug access.
 - 1.3 Supportive instruments required to support each of the activity.
 - 1.4 Actors required to participate in the stage of agenda setting and the actors' role
2. What were policy elements essential in the stage of policy formulation, and why they were essential:
 - 2.1 Contextual elements required to support the policy formulation of CL policy.
 - 2.2 Activities required to formulate the CL policy.

- 2.3 Supportive instruments required to support each of the activity.
 - 2.4 Actors required to participate in the stage of policy formulation and the actors' role
3. What were policy elements in the policy implementation, and why they were essential:
- 3.1 Contextual elements required to support the implementation of CL policy.
 - 3.2 Activities required to implement the CL policy.
 - 3.3 Supportive instruments required to support each of the activity.
 - 3.4 Actors required to participate in the stage of policy implementation and the actors' role.
4. What were policy elements in the policy monitoring, and why they were essential:
- 4.1 Contextual elements required to support the monitoring and evaluation of CL policy.
 - 4.2 Activities required to monitor the CL policy performance and evaluate its implications.
 - 4.3 Supportive instruments required to support each of the activity.
 - 4.4 Actors required to participate in the stage of policy monitoring and evaluation and the actors' role.
5. Additional issues of concerns: Would you like to add other issues of concerns?

Second, in the stakeholder meeting, I used observational guides as the table below. I made matrix, which includes the same contents as the interview topic questions mentioned above, in order to facilitate in data collection.

Observation category	Contents			
Settings	Describe the whole context/meetings, layout on seating plan of people present			
Participants and their relationship	Who are in the settings? What are their roles?			
Participants' information	What do they mention about the policy elements relevant to the CL policy according to the matrix below			
Key elements	Agenda setting	Formulation	Implementation	Monitoring
Contextual elements				
Participant No.1.				
Participant No.2				
Participant ...				
Activities				
Participant No.1.				
Participant ...				
Supportive instruments				
Participant No.1.				
Participant ...				
Actors				
Participant No.1.				
Participant ...				
Additional issues of concerns				
Participant No.1.				
Participant ...				